Perceived Medical Error in Primary Care: Physicians' remorse and patients' view

—The need for a moral perspective in the analysis of medical harm

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Patient safety and quality improvement in healthcare delivery are the priority for the healthcare profession in Japan as well as elsewhere in the world. Analogous to the Dana Faber incident in Boston, the nation-wide awareness of safety issues in healthcare was triggered by an incident in 1999 at a Yokohama hospital where surgical operations were performed on the wrong patients.

Since then, safety managers and incident reporting have been mandated for major public hospitals, and institutional system failure behind the errors committed by the individuals involved has been emphasized and a "no blame culture" has begun to evolve in implementing safer systems in hospitals. Two epoch-making IOM reports[1,2] have been translated into Japanese, and the Japanese Society for Quality and Safety in Healthcare has recently been founded as well.

Behind the patient safety issue, however, there is the feeling of guilt for patients who have suffered unnecessary loss of life or ill health due to a "silly" mistake of a provider of healthcare, be it a physician, nurse or allied healthcare professional. In this issue, Miyasaka et al.[3] present vivid accounts of remorse and regret expressed by a small group of conscientious Japanese primary care physicians regarding the most memorable medical error committed and its perceived causes through a semi-structured interview with an instrument developed by Ely and Levinson some years ago.[4]

While the authors found minor differences such as financial implications and fear of litigation, Japanese primary care physicians face similar clinical situations to those faced by US physicians. In this well executed qualitative study, the main error was diagnostic and procedural, and the participants had a high sense of responsibility. Poor judgment and insufficient knowledge and skill occupy the physicians mind even after so many years. I would like to know more about how they faced the situation and how they responded to the bewilderment and anger of those who suffered, and the sorrow of their family.

According to Sharpe,[5] throughout the historical development of the idea of "iatrogenesis," the patients' perspective has increasingly been incorporated in the discussion of medical harm. Similarly, drawing upon religious traditions of Western societies, N. Berliner, an ethicist at the Hastings Center, reminds us of the importance of the patients' perspective in discussing the "no blame culture" citing the Janus-faced idea of forgiveness, and advocates a new theory of forgiveness.[6] We should be forgiven by patients before we can forgive each other, and the cultural and religious background of society has strong implications.

As a responsible learning profession,[7] we should be more attentive to moral issues raised by medical harm. To spare our patients from unnecessary injury, we should develop the habit of reflection-in-action upon our everyday performance not only as clinicians but as responsible members of the healthcare community.

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Original Article

Japanese Primary Care Physicians' Errors and Perceived Causes: A comparison with the United States

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Abstract

Background   Reducing medical errors will improve health care quality, though few studies have addressed errors in Japan. We investigated primary care physicians' medical errors and perceived causes. We compared the results with previously reported U.S. data.

Methods   Using a semi-structured instrument, we interviewed Japanese physicians about their most memorable medical errors and the perceived causes. We qualitatively analyzed interview transcripts to describe the errors and causes using a taxonomy including the categories: clinician factors, communication factors, administration factors, blunt-end factors, and patient-related factors.

Results   Thirty-three Japanese primary care practitioners participated. Of 37 reported cases, 15 occurred in hospitals, and 22 occurred as outpatients. Misdiagnoses (n = 10) and procedural complications (n = 7) were the most commonly reported errors. The most commonly reported causes included being hurried/busy (n = 19), underestimating the patient's condition (n = 13), lack of follow-up (n = 12) and being distracted (n = 10). Cost and legal issues were raised as concerns less than in a similar U.S. study.

Conclusions   The most common memorable medical errors reported by Japanese physicians included misdiagnoses and procedural complications. The causes of being hurried and lacking knowledge were found in similar proportions to a previous U.S. study. Socio-cultural differences between Japan and the U.S. such as legal and insurance system differences appear to influence physicians' perceptions of medical errors. These data demonstrate that serious medical errors occur in both inpatient and outpatient settings in Japan, and that primary care physicians can recognize and will discuss their errors. Further research is needed on epidemiology of and prevention of medical errors in Japan.

Key words   Medical error, Cultural comparison, Japan, Primary care, Health care quality

Introduction

As illustrated by two Institute of Medicine reports, investigation of medical errors and their causes is essential to improve the quality of heath care.[1,2] While previous studies cite the significance of error in primary care, the most important etiologies of harm remain poorly understood.[3,4] Given the wide variety of services rendered by primary care physicians and their critical role in the health care system, under-

standing errors by primary care practitioners is particularly important.[3]

Previous work relevant to primary care physicians includes self-reports of error,[5,6] reports on generalists' errors in prescribing long-term medications,[7] research on the emotional impact of errors and physicians' willingness to support colleagues involved in an error or other adverse event,[8] and patients' preferences for management of medical errors based on theoretical cases.[9] Conradi and colleagues conducted a series of pioneering studies on error in Dutch general practice.[10] Few studies have taken a population-based perspective[11–13] and these have limitations.[3] Also important are the taxonomies used to classify medical errors in primary care, as these are needed to rigorously study the phenomenon.[3,14–16] Despite the progress of research in this field, examination of errors by primary care physicians in Japan has been lacking, and little research addresses how cultural differences could affect medical errors.[13]

Wocher's work in the Japanese literature provides personal observations and analysis of quality of medical care and errors in Japan.[17] Other recent work on medical errors in Japan focuses on the need for system-based changes, such as central error reporting and the use of computerized systems for promoting a culture of patient safety.[18–21] However, these works focus on university/large hospital settings. We were unable to identify previous studies examining medical errors by primary care physicians in Japan.

In this study, we sought first to identify the kinds of errors Japanese primary care physicians have experienced, and second to understand their perceived causes of those errors. As we employed a design previously utilized in the United States (U.S.),[5] a third objective was to compare our results from Japan with the previous study, and to consider social and cultural influences.

Methods

This qualitative study used semi-structured interviews[22] and a series of structured questions. The University of Michigan Institutional Review Board approved this study.

The study subjects were Japanese general practitioners recruited throughout Japan. We recruited using snowball sampling,[23] starting with three Japanese physicians known to us. In the snowball sampling method, participants are accrued through introductions from previous participants.[23] The use of personal contacts is essential to conduct such sensitive research in Japan[24] and this greatly facilitated cooperation of recruited physicians.

We conducted a review of cultural categories (a process for recognizing personal biases used in qualitative research) and identified a broader number of issues for investigation than any one of us would have identified individually.[25] Specifically, we felt Japanese physicians in solo practice would be reluctant to discuss errors, except with very careful assurances and personal contacts. We postulated that the social impact of revealing errors, particularly with regard to shame, merited consideration based on physicians having high social status. We felt that malpractice considerations might be very different.

The structured questions portion of the interview followed the format used by Ely et al. (Appendix 1).[5] We asked subjects to rate 20 possible causes on a 4-point Likert scale developed by Ely et al.[5] We also asked subjects about events, such as malpractice claims, patient or family anger, and whether any outside institution was involved in handling the consequences of the event.

One of us (EAM) conducted the interviews in Japanese with the participating physicians in June and July of 2003. In accordance with the human subjects protocol, we did not obtain written consent to protect participant confidentiality. During the open-ended portion of the interview, we asked the physician to describe an event that s/he considered her/his most memorable medical error or near-error, and list factors s/he thought contributed to that error. We did not limit discussions to the inpatient or outpatient setting. Participants then answered the structured, Likert-scale questions. The interview closed by asking the interviewee for any other comments. Each interview was performed during off-hours in the physicians' offices, and lasted between 20 and 40 minutes. The interviews were electronically audio-recorded, and transcribed using a selective transcription procedure by one of the researchers (EAM) (interjections such as "um" and "uh" were not transcribed).[26,27] We erased the recordings after transcription to protect participant confidentiality. One of us (EAM) translated the transcripts into English, and two of us (AK and MDF) checked these for accuracy.

Table 1 Demographics of participating Japanese physicians and location of where reported errors occurred

Participating physicians (N = 33)	Mean	Range
Age	52	38–76
Physician characteristics	n	%
Male	30	91
Pediatricians	25	76
Other specialties	8	24
Location of reported cases (N = 37)	n	%
Occurred in private practice	22	59
Occurred in hospital setting	15	41

In the analysis, we grouped the physicians' perceived causes of the errors using a classification system combining elements of taxonomies from previous authors.[3,5,15,16] We considered their reports an "error" if the interviewed physician thought that it was an error, even though clinicians did not always distinguish between adverse events and errors. Error implies a mistake is made, though adverse events, namely bad outcomes, can occur as a complication with or without a medical mistake. We used findings from the qualitative analysis to corroborate the findings from the structured interview questions, and to develop a more in-depth understanding of the cases. We conducted member checking[26] by distributing a Japanese summary of the findings by email to participants who provided an address. Responses revealed general agreement, and no concerns that we hadn't raised already.

Results

We interviewed 33 physicians with training in various fields including anesthesiology, cardiology, ENT, general medicine, general surgery, neurology, obstetrics and orthopedics. All were private practitioners ranging from 1 to 36 years experience in private practice, and 15 to 62 years total practice. The age of the physician at the time of the incident ranged from 24 to 75, and their current ages ranged from 38 to 76. The physicians' practice locations had a wide geographic distribution over Japan from Kagoshima to Sendai in both urban and rural locations. Twenty-five of the 33 participants were pediatricians. Three participants were female. All participants reported sub-specialty training, but prac-

tice as generalists (Table 1). One physician could not recall any errors. Five physicians voluntarily recalled two incidents. Four reported cases were near-misses without adverse outcomes. In three cases, the physical acts of the errors were committed by a nurse or another physician, but the interviewed physician took responsibility since her/his role was as supervisor. Fifteen of the 37 reported incidents occurred in a hospital setting before entering private practice (range 1 to 20 years after graduation, mean 5 years) and 22 occurred after entering private practice (range 1 month to 35 years, mean 8 years) (Table 1).

The errors and causes

A summary of the errors elicited is listed in Table 2. Many misdiagnoses were surgical in nature. While only five cases of vaccination errors were reported as a most memorable error, four more such cases were mentioned during the interviews. Similarly, while only four medication errors were cited as most memorable during the interviews, three other physicians specifically mentioned having committed errors in giving medications, with one of them saying "I'm sure I've made 10 or 20, well, maybe even more 'oops'es with writing prescriptions."

The most common contributing factors to the reported errors were the sense of being hurried (19 cases, 51%), underestimating the patient's condition (13 cases, 35%) and lack of a good follow-up plan (12 cases, 32%). Through qualitative analysis, we classified the causes of errors into five categories: physician-related factors, communication factors, administrative factors, blunt-end factors, and patient-related factors (Table 3). A mean of 4.4 causes per case was

Table 2 Types of errors reported by Japanese primary care physicians*

	n
Misdiagnoses (N = 10, 27%)	
Missed appendicitis	3
Missed cancer on imaging study	2
Misdiagnosed meningitis as a cold	1
Missed intussusception	1
Missed subarachnoid hemorrhage	1
Missed testicular torsion	1
Other misdiagnosis	1
Procedural complications (N = 7, 19%)	
Pneumothorax from placing a central line	2
Nerve damage from injection or IV line	2
Infectious complication from blood transfusion	1
Bleeding complication from a procedure	1
Patient's injuries worsened during resuscitation procedures	1
Vaccine errors (N = 5, 14%)	
Gave the wrong vaccine	3
Gave the wrong person the vaccine (e.g. mixing up brothers)	2
Drug errors (N = 4, 11%)	
Wrote for or gave a wrong dose of a medication	3
Gave a different drug with a similar name	1
Communication errors (N = 3, 8%)	
Caretaker inadequately warned about the dangers of the patient's medical condition	2
Treatment plan changed while doctor was away, and the patient died	1
Other errors (N = 8, 22%)	
Doctor thought s/he mismanaged a patient, in retrospect	5
Patient had a bad outcome despite no obvious source of error	3

*Details of some errors are not fully disclosed to protect participant confidentiality.
Percentages do not add up to 100% due to rounding.

reported by the physicians (range 1 to 10).

The qualitative findings enrich understanding of the factors within the five categories of errors identified from the interviews:

Physician-related factors

Five participants mentioned a general lack of experience as a factor in their incident.

"Well, it was the lack of experience, and there was nobody to instruct and help us, but we still had to make the decision on our own... maybe we should have just waited and thought about what to do, but we didn't really know the cause, and even thought that it might be heart failure. But, there's no way a 2nd year doctor could make that kind of decision. It's a scary story now that I think back on it."

An interesting anecdote by one physician illustrates the subtlety of distraction:

"No, well, it's not exactly that I was distracted.

As I was going around a very busy emergency ward, I was telling myself to pay attention, so subjectively, I don't think I was distracted, but from an outside perspective, something may have been wrong."

Communication factors

Breakdowns in communication contribute to medical errors. Two physicians thought that they did not clearly instruct their patients about certain aspects of their diseases. For example, one doctor mistakenly assumed that the patient's mother understood everything that he told her, such as not using unnecessary antipyretics on a child with a mild fever. This lack of communication resulted in an adverse event affecting the child.

Administration factors

Six physicians brought up flaws in the system as factors in their incident. For example, one

Table 3 **Factors contributing to the reported errors: A comparison of Japanese physicians' reports and U.S. physicians' reports in a previous study[5]**

Japan (N=37), U.S. (N=53)	Japan n (%)*	U.S.[5] n (%)*
Physician stressors		
Physician hurried or busy	19 (51)	30 (57)
Physician distracted	19 (27)	25 (47)
Physician fatigued	5 (14)	16 (30)
Physician influenced by others' opinions	5 (14)	20 (38)
Time was stressful for physician (e.g. on call, weekend, "quitting time")	3 (8)	22 (42)
The nature of the relationship with the patient interfered with proper care (too familiar or too unfamiliar)	3 (8)	7 (13)
Physician angry in general	1 (3)	NM
Physician was busy with non-clinical work	1 (3)	NM
Deficient knowledge		
Underestimated patient's condition	13 (35)	19 (36)
Lack of knowledge about medical aspects of the case or disease	11 (30)	26 (49)
Lack of experience in general	5 (14)	NM
Physician did not take an adequate history, or did look at history enough	2 (5)	11 (21)
Physician did not perform adequate physical	1 (3)	9 (17)
Physician lacked knowledge on resuscitation	1 (3)	NM
Physician did not perform necessary tests	1 (3)	NM
Deficient judgment or cognitive skills		
Lack of good follow-up plan	12 (32)	18 (34)
Inadequate differential diagnosis or development of diagnostic possibilities	8 (22)	26 (49)
Physician did not ask advice	8 (22)	11 (21)
Physician missed important symptoms	7 (19)	NM
Physician did not check available test results	3 (8)	1 (2)
Other clinician factors		
Execution error ("stupid mistake")	7 (19)	NM
Physician relied on technology	4 (11)	NM
Physician was misled by benign symptoms	2 (5)	22 (42)
Physician did not want to burden patient with extra costs	1 (3)	NM
Physician hesitated	1 (3)	NM
Testing facilities/technician not available	1 (3)	NM
Supervisor unavailable	1 (3)	NM
Communication factors		
Physician did not adequately instruct patient	2 (5)	NM
Physician did not communicate patient information to covering doctor well enough	1 (3)	NM
Patient shy about symptoms	1 (3)	NM
Administration factors		
Immunization system was flawed (e.g. forms were the same color)	4 (11)	5 (9)
Testing facilities/technician not available	1 (3)	NM
Supervisor unavailable	1 (3)	NM
Others administration factors		
Nursing procedural skills error	2 (5)	NM
Lack of supervision of staff	2 (5)	NM
Primitive equipment	1 (3)	NM
Nurse picked up wrong medication	1 (3)	NM
Blunt end factors		
Understaffed institution	2 (5)	NM
Lack of beds at institution	1 (3)	NM
Patient-related factors		
Inaccurate information from patient	4 (11)	NM
Patient with similar name came in	2 (5)	NM
Distracting patient behavior	2 (5)	NM
Patient asked to not be hospitalized	1 (3)	NM
Patient's mother had psychiatric issues	1 (3)	NM

Sub-categories do not add to 100% as multiple responses were possible.
The numbers in U.S. column represent data from the study by Ely et al.[5]   NM: factors not mentioned in the study by Ely et al.[5]

physician, who recalled an incident while in a university setting, thought that limited access to laboratory testing was the biggest contributing factor. The physician attempted to obtain an important diagnostic study after hours, but the laboratory was closed. A hospital decision not to staff the laboratory after normal business hours illustrates an administration factor.

Blunt-end factors

Blunt-end factors are those that are indirectly associated with errors, and in general include things such as insurance or government regulations, and staffing or geographical limitations. Two physicians mentioned being under-staffed as a factor in their incident. One doctor recalled an incident that happened just after opening a new practice. At the time, the new clinic did not have enough staff, and the physician administered the wrong treatment to the wrong patient. The blunt-end factor in this case is the lack of staffing.

Patient-related factors

Some physicians mentioned patient factors contributing to the reported incidents. For example, one physician described administering a vaccination intended for one child to his sibling who looked similar and also had a nearly identical name. The characteristics of the patients, in particular their similar looks and names, are the patient-related factors in this case.

It is important to note that multiple factors can simultaneously contribute to a single error. For example, consider a case where a physician inadvertently administers a vaccination to the wrong sibling. The setting involves a new practice, the physician barely knows the patients, and there is inadequate staffing. It can be said that physician factors, patient-related factors and blunt-end factors contributed to the error. The physician factor is that s/he did not know the patient well. The patient-related factors are that the siblings looked alike, and had similar names. The lack of staffing to confirm patient identity illustrates a blunt-end factor. Errors are often consequences of multiple factors, and it is sometimes hard to identify an exclusively causative factor for a given error.

Outcomes of errors

Thirteen incidents directly or indirectly resulted

Table 4 Japanese physicians' assessments of the outcomes, reason for being memorable, and perception of fault for the reported errors

Outcomes of cases (N = 37)	n	%
Death	13	35
Permanent disability	4	11
Temporary disability	4	11
No adverse outcome	16	43
Reason for being memorable (N = 37)	n	%*
Bad outcome for patient	11	30
"Stupid" error	5	14
First error in new environment	5	14
Other	16	43
Perception of fault (N = 37)	n	%
Completely at fault	16	43
Mostly at fault	10	27
Partially at fault	10	27
Not at fault	1	3

*Percentages do not add up to 100% due to rounding.

in the patient's death. Four patients suffered permanent disability, and four others were temporarily in serious condition. The remaining 16 cases involved full patient recovery without a serious outcome (Table 4).

Eleven of the incidents were memorable due to a bad outcome. Five were memorable because the physician thought the error was stupid or unthinkable, and five others were memorable because it was the first in the physician's career or the first after entering private practice (Table 4).

In 16 cases, the physicians believed they were at fault. Ten felt they were mostly at fault, ten felt partially at fault, and one denied fault. Three physicians remarked that although they were clearly at fault, they would understand if another physician made a similar error.

Only one case had legal involvement, and four cases involved outside institutions, such as the district public health office or the physician's union that were contacted by a person involved in the event.

Discussion

The most common types of errors reported by these Japanese primary care physicians were misdiagnoses and procedural complications. Like our findings, the most common type of errors reported in Ely's U.S. study[5] were delayed or

missed diagnoses. These were mostly medical in nature (e.g., missed cancer, missed myocardial infarction). This difference may be due to the more homogeneous sample of family physicians in the Ely study, and the large proportion of pediatricians of various specialty training in our study. Surgical and medical mishaps were the second most common class of errors in Ely's U.S. study,[5] just as procedural errors were in our results. Similar to Dovey's report[13] showing communication errors were more commonly reported by general practitioners in other countries (Australia, Canada, England, Netherlands, New Zealand) than the U.S., these results from Japanese physicians also emphasize communication errors more than the U.S. Medication errors were the most commonly reported type of error overall in Dovey's report,[13] but their data are for errors overall, not just the most memorable ones. While we identified minor differences in perceived causes, we found the major sources of errors, such as being hurried and lacking knowledge, in similar proportions to the Ely study.

In the primary care setting, the causes of errors, like being hurried, are the product of a system basically organized around a one-on-one interaction between the patient and doctor. Continuity and the doctor-patient relationship may contribute to error prevention in primary care. However, there may be less structured or different checks-and-balances needed in primary care compared to the hospital setting. This highlights the need for a system-based approach to improve safety in the primary care setting. System-based approaches can involve automating procedures, developing computer support systems, and building redundancy into systems. An example of a simple system-based change is the use of color-coded forms for immunizations rather than monochromatic forms to facilitate record finding and preventing immunization errors.

Physicians felt strongly responsible for their actions. In the cases where nursing procedural skill errors were involved, the physicians, as the supervisor, still took full responsibility. This parallels the high sense of responsibility in caring for patients among U.S. physicians reported by Wu et al.[28]

A major difference between the result of this study and the Ely study[5] is that treatment cost seemed hardly a consideration in Japan. Six physicians in the Ely study[5] avoided an intervention because of its cost while only one Japanese physician mentioned cost as a contributing factor. This is likely attributable to the national insurance system in Japan, where the patients are responsible for only a fraction of medical costs. Also, reimbursement is directly related to the number of cases seen, and less correlated with the complexity of the cases. Low reimbursement rates incentivize seeing many patients, much more so than in the U.S. Furthermore, while health care in Japan is characterized by unrestricted access to any physician, physician specialization in primary care fields is not well developed as sub-specialty trained physicians can enter into primary care practice at anytime without restriction. Patients self-select the institution they visit, and it appears patients have more outpatient visits for specialty care in Japan[29] than the U.S.[30]

These complex system differences render direct comparisons between the two countries difficult and should be done cautiously. However, based on this study in Japan and the U.S. study by Ely,[5] we opine the following are important cultural and system differences relevant to medical errors. The legal contexts of Japan and the U.S. vary dramatically. While few Japanese physicians expressed concern with legal issues, legal considerations seem to weigh prominently upon the minds of U.S. physicians.[31] This is not surprising given there are fewer lawyers and fewer occurrences of malpractice litigation in Japan.[32] Second, physicians in both countries have a strong sense of responsibility, though a physician who admits to an error may be judged more harshly in Japan than in the U.S. This may be related to the particularly high status physicians hold in Japanese society and the 'height of the fall' would seem to be greater in Japan. In the eyes of a Japanese public expecting infallibility, admission of an error would seriously compromise one's credibility in the community. Third, from a structural perspective, Japanese primary care physicians are generally not expected to take a stewardship role in provision of preventive services. A notable exception is childhood immunizations, though even these are frequently provided in the public health sector rather than by physicians. Fourth, mandatory informed consent for procedures in the U.S. calls for a discussion of the benefits and risks, and hence, bad

outcomes, that could occur. While informed consent continues to take a greater a foothold in Japan,[33] it is not as pervasive or explicit as in the U.S. When used, this formal *a priori* communication forewarns U.S. patients of the risks for harm. This may render after the fact disclosure of bad outcomes, both complications and errors, easier in the U.S. than in Japan.

Limitations of this study include the lack of a precise definition of "medical error" provided to the participants as some described events not fitting the IOM[2] criteria of a "medical error." We made this procedural choice to allow a comparison of our findings with the Ely study.[5] Some of the events described would fall under the category of an unfortunate, but unpreventable event with an adverse outcome, rather than a preventable error. Increased awareness of what constitutes a medical error is needed.

Another limitation of this study is that some incidents occurred when the physician was a house officer in a university or major hospital setting, and not a primary care setting. The Ely study also contained errors described by physicians while they were house officers.[5] While this may not reflect the current practice setting of primary care physicians, we believe that the data still shed insight into how physicians perceive causes of errors within a different culture and health care system. A large number of participants are pediatricians, though almost all include a significant general practice component in their work. Care must be exercised in generalizing these findings to other private practitioners in Japan. Still, these physicians' experiences were real, and provide a previously unavailable window into the types and perceived causes of errors experienced by primary care physicians in Japan.

Conclusion

The most common memorable medical errors reported by these Japanese physicians included misdiagnoses, procedural complications, vaccination mishaps and medication errors. The most commonly reported causes of these events included being hurried/busy, underestimating the patient's condition, lacking a follow-up plan, and being distracted. Though cost of care and litigation concerns are important factors for U.S. physicians, these were infrequently volunteered as important by Japanese physicians. We hypothesize socio-cultural factors influence physicians' perceptions of the occurrence, causes and resolution of medical errors in Japan. Specific areas include: the high status of physicians, the culture of shame, differences in training backgrounds of primary care physicians, and a weaker foothold of informed consent. Finally, these data demonstrate that serious medical errors occur in both inpatient and outpatient settings in Japan, and that primary care physicians can recognize and will discuss their errors. Further research on the epidemiology of and prevention of medical errors is needed to improve health care quality in Japan.

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Appendix

Closed-ended portion of the survey instrument, used with permission from Ely[5]*

I will now ask you about a list of factors that may or may not have been involved in your case. These factors were mentioned as possibly related to the most memorable errors of other physicians. Some factors on this list may not apply in your case. Please answer yes, no or not applicable to each of the factors, and if yes, please also answer how important it was on a 4-point Likert scale.

Factor	1. Not a factor at all	2. Possibly a minor factor	3. A definite but less important factor	4. A major factor
1. Were you fatigued? Yes/No				
2. Did you have a sense of being distracted? Yes/No				
3. Did you have a feeling of being hurried? Yes/No				
4. Did you have any feelings of dislike for the patient or family? Yes/No				
5. Was there any lab work or x-rays that you remember ordering but then not checking after it had been ordered? Yes/No				
6. Did you have any feelings of anger (e.g. anger with patient, nurse, family or just in general)? Yes/No				

How important do you think the following, possibly contributing, factors were in this case?

Factor	1. Not a factor at all	2. Possibly a minor factor	3. A definite but less important factor	4. A major factor
1. Lack of knowledge about the medical aspects				
2. Being too cost conscious				
3. Hesitating too long				
4. Over reliance on others' opinions				
5. Too much trust in technology; i.e., going with technology rather than your own clinical impression				
6. Reaching beyond your own capabilities				
7. Not asking advice				
8. Not taking patient seriously enough				
9. Having too much pride				
10. Prematurely closing your mind				
11. Not having an adequate follow-up plan				
12. Not following up a seemingly minor complaint				
13. Not taking an adequate history				
14. Not doing an adequate physical exam				

*The translated Japanese survey instrument is available upon request.

Original Article

The Significance of Home Blood Pressure Measurement in Patients with Chronic Kidney Diseases

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Abstract

Background and Purpose   While assessment of home blood pressure (HBP) is considered to be important for the diagnosis and treatment of hypertension and the prevention of cardiovascular diseases in the general population or treated hypertensive patients, the value of HBP measurement in patients with chronic kidney diseases (CKD) has not been investigated in detail. We examined BP control based on HBP and clinic BP (CBP) and the association with the CKD stage or underlying diseases in CKD patients.

Methods   We obtained HBP recordings from 221 CKD patients with a creatinine clearance (Ccr) of less than 90 ml/min/1.73 m² treated with antihypertensive drugs in the nephrology department in a university hospital. HBP was defined as the mean value of morning and evening BP on 7 consecutive days. The patients were divided into 3 groups according to Ccr: Group A; ≧60 ml/min/1.73 m² (n=48), Group B; ≧30 and <60 ml/min/1.73 m² (n=79), and Group C; <30 ml/min/1.73 m² (n=94).

Results   The prevalence of systolic HBP≧135 mmHg and systolic CBP≧140 mmHg (sustained hypertension) was 27.1%. The prevalence of systolic HBP≧135 mmHg and systolic CBP<140 mmHg (masked hypertension) was 25.3%. While the average HBP was 135/78 mmHg in Group A, 134/77 mmHg in Group B and 141/77 mmHg in Group C (systolic HBP; Group C vs. A $P<0.05$, Group C vs. B $P<0.01$), systolic CBP was not significantly different in the 3 groups. Systolic HBP was higher in patients with diabetic nephropathy than in those with non-diabetic renal diseases in each group.

Conclusions   A significant proportion of CKD patients have sustained and masked hypertension discovered by HBP measurement. HBP control was less satisfactory in patients at an advanced stage of CKD or those with diabetic nephropathy. HBP measurement is essential for better BP control in CKD patients.

Key words   Home blood pressure, Chronic kidney disease, Masked hypertension

Introduction

Home blood pressure (HBP) measurement is widely available and has numerous advantages over control of BP based on clinic BP (CBP) in the management of hypertension.[1,2] BP assessment based only on CBP often misclassifies hypertension. Many normotensive or hypertensive patients still have elevated HBP in spite of good control of CBP, and this is called "masked hypertension."[3–6] HBP has more predictive power than CBP in target-organ damage and cardiovascular events in the general population or treated hypertensive patients.[7–9] Thus, BP control based only on CBP in hypertensive patients is not only insufficient but also lacking in reliability.

Strict BP control is important in limiting decline in renal function and to lessen the occurrence of cardiovascular events in patients with

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Table 1 Clinical characteristics of patients

	All subjects (n = 221)	Group A (n = 48)	Group B (n = 79)	Group C (n = 94)
Age (years)	62.7 ± 12.5	60.9 ± 12.8	61.4 ± 12.4[a]	64.7 ± 12.2[a]
Male (%)	164 (74.2)	36 (75.0)	59 (74.7)	69 (73.4)
Underlying disease				
Non-diabetic renal diseases (%)	144 (65.2)	36 (75.0)	52 (65.8)	56 (59.6)
Chronic glomerulonephritis	82	22	28	32
Nephrosclerosis	46	13	18	15
Polycystic kidney disease	9	0	5	4
Others	7	1	1	5
Diabetic nephropathy (%)	77 (34.8)	12 (25.0)	27 (34.2)	38 (40.4)
Body mass index (kg/m^2)	23.8 ± 3.3	24.4 ± 3.4	24.0 ± 3.3	23.3 ± 3.2
Serum creatinine (mg/dl)	2.85 ± 2.13	1.17 ± 0.34	1.85 ± 0.43[a]	4.54 ± 2.31[b,c]
Creatinine clearance (ml/mim/1.73 m^2)	38.5 ± 23.5	73.7 ± 8.2	43.7 ± 8.5[b]	16.2 ± 6.8[b,c]
Hematocrit (%)	35.4 ± 6.2	39.5 ± 5.6	37.2 ± 5.3[a]	31.8 ± 5.3[b,c]
Urinary protein excretion (g/day)	1.79 ± 1.92	1.27 ± 1.29	1.89 ± 2.15	1.98 ± 1.95[a]

a; $P<0.05$ vs Group A, b; $P<0.001$ vs Group A, c; $P<0.001$ vs Group B

chronic kidney diseases (CKD).[10,11] The current guidelines recommend that BP be maintained at lower levels in CKD patients than in the general population, and the goal BP is less than 130/80 mmHg.[2,12] HBP measurement may also be of value in improving BP assessment in CKD patients. Recently, a study in United States showed that 26–29% of CKD patients had masked hypertension based on ambulatory BP monitoring.[13] However HBP has not been fully investigated, and the prevalence of masked hypertension is not clear in Japanese CKD patients. In addition, the relationship between the CKD stage or underlying renal diseases and HBP control is also unclear in these patients. Therefore, we examined BP control based on HBP and CBP and tried to clarify the significance of HBP measurement in Japanese CKD patients.

Patients and Methods

Patients

The study subjects included all 221 patients who met the eligibility criteria among those who were treated in the nephrology department of Tokyo Medical University Hospital in Tokyo between November of 2003 and June 2005. The inclusion criteria were as follows; they were receiving antihypertensive treatment, they had already performed HBP measurement by themselves, they

had been treated for at least 3 months at this clinic, a 24-hour urine collection had been made, and their creatinine clearance (Ccr) was less than 90 ml/min/1.73 m^2. The exclusion criteria were as follows; they had non-diabetic renal diseases complicated with type 2 diabetes mellitus, they had changes in antihypertensive drugs within 2 weeks before BP data collection, they received dialysis therapy, or their HBP data were judged to be inadequate or inaccurate. Four doctors treated the subjects according to the current guidelines for BP control. We set up a goal BP of nearly 130/80 mmHg both at home and in the clinic, or at least less than 135/85 mmHg at home and less than 140/90 mmHg in the clinic. The number of patients was not very different between each doctor. Informed consent to use the clinical data in this study was obtained from all the patients.

The patients were divided into 3 groups according to the classification based on the CKD staging presented by Kidney Disease Outcome Quality Initiative:[14] Group A; Ccr≧60 ml/min/1.73m^2 (CKD stage 2, n=48), Group B; Ccr≧30 and Ccr<60 ml/min/1.73 m^2 (CKD stage 3, n=79), and Group C; Ccr<30 ml/min/1.73 m^2 (CKD stage 4 or 5, n=94). Details of patient clinical characteristics and antihypertensive treatment in each group are listed in Table 1 and 2, respectively. Diabetic nephropathy was judged from

Table 2 Characteristics of antihypertensive treatment

	All subjects (n = 221)	Group A (n = 48)	Group B (n = 79)	Group C (n = 94)
Number of drugs				
1	58 (26.3%)	15 (31.2%)	22 (27.8%)	21 (22.3%)
2	90 (40.7%)	21 (43.8%)	36 (45.6%)	33 (35.1%)
3 or more	73 (33.0%)	12 (25.0%)	21 (26.6%)	40 (42.6%)
Class of drugs				
Furosemide	65 (29.4%)	3 (6.3%)	20 (25.3%)	42 (44.7%)
Calcium channel blocker	154 (69.7%)	30 (62.5%)	50 (63.3%)	74 (78.7%)
Angiotensin receptor blocker	156 (70.6%)	35 (72.9%)	65 (82.3%)	56 (59.6%)
Angiotensin converting enzyme inhibitor	79 (35.7%)	20 (41.7%)	30 (38.0%)	29 (30.9%)
Time of administration				
Morning only	102 (46.2%)	28 (58.3%)	44 (55.7%)	30 (31.9%)
Morning and evening	112 (50.6%)	19 (39.6%)	34 (43.0%)	59 (62.8%)
Evening only	7 (3.2%)	1 (2.1%)	1 (1.3%)	5 (5.3%)

renal biopsy or medical history (duration of illness and presence of overt proteinuria and diabetic retinopathy).

CBP measurement

CBP was measured by a nurse using a mercury sphygmomanometer. The patients were seated with their backs supported for at least 2 minutes before the measurement and their arm was supported at heart level. The value of a single measurement was recorded as CBP in each patient.

HBP measurement

HBP was measured according to the guidelines of HBP measurement of the Japanese Society of Hypertension.[2] HBP was measured using a semiautomatic arm device. The patients were seated with their backs supported for at least 1 minute before the measurement and their arm was supported at heart level. HBP was measured in the morning within 1 hour of waking and before taking antihypertensive drugs and in the evening just before going to bed. The value of a single measurement was recorded each time. The patients recorded their HBP for 7 consecutive days until the day just before the visit to the hospital. The HBP value for each patient was calculated as the mean values of morning and evening BP over those 7 days (a total of 14 measurements).

The patients were instructed how to use the semiautomatic arm devices accurately by nurses.

The accuracy of these devices and the ability of the patient to measure BP were checked by the nurses.

Other data collection

A 24-hour urine specimen was collected within the 7-day period of HBP measurement before the visit to the hospital. Ccr, urinary sodium and protein excretion were measured.

Classification of hypertension according to HBP and CBP

We evaluated systolic BP and diastolic BP separately.

Sustained hypertension:
  Systolic BP;
    HBP≧135 mmHg and CBP≧140 mmHg
  Diastolic BP;
    HBP≧85 mmHg and CBP≧90 mmHg
Masked hypertension:
  Systolic BP;
    HBP≧135 mmHg and CBP<140 mmHg
  Diastolic BP;
    HBP≧85 mmHg and CBP<90 mmHg
White-coat hypertension:
  Systolic BP;
    HBP<135 mmHg and CBP≧140 mmHg
  Diastolic BP;
    HBP<85 mmHg and CBP≧90 mmHg
Controlled:
  Systolic BP;
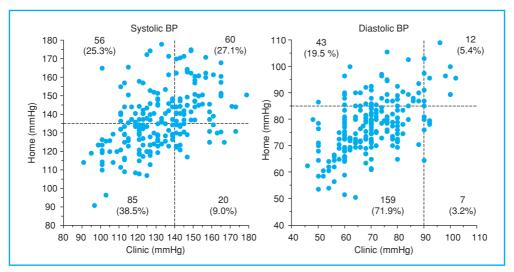   HBP<135 mmHg and CBP<140 mmHg

Fig. 1 Distributions of Home and Clinic BP

Table 3 Percentages of patients' categories according to recommended BP (130/80 mmHg)

		Clinic BP				
	Systolic	≧130 mmHg	<130 mmHg	Diastolic	≧80 mmHg	<80 mmHg
Home BP	≧130 mmHg	95 (43.0%)	49 (22.2%)	≧80 mmHg	34 (15.4%)	54 (24.4%)
	<130 mmHg	25 (11.3%)	52 (23.5%)	<80 mmHg	17 (7.7%)	116 (52.5%)

Diastolic BP;
   HBP<85 mmHg and CBP<90 mmHg

Study protocol

We examined the distribution of HBP and CBP in all subjects. We classified the subjects into 4 groups according to the classification of hypertension described above and examined each prevalence. We compared HBP and CBP among the 3 Ccr groups. In addition, we compared these data between patients with diabetic nephropathy (DN) and those with non-diabetic renal diseases (nDN) in each Ccr group. Furthermore, we examined the influence of anemia or erythropoietin treatment. Finally, to assess dietary salt intake, we examined urinary sodium excretion in each Ccr group.

Statistics

The data were expressed as mean ± SD. A *P* value of less than 0.05 was considered to indicate a statistically significant difference. The two groups were compared by the Mann-Whitney test, and the three groups were compared by one-way analysis of variance. The chi-square test was also used. Correlation between two values was analyzed by Pearson's correlation coefficient.

Results

Distribution of HBP and CBP (Fig. 1)

HBP and CBP significantly correlated (Fig. 1, systolic BP; r = 0.470, diastolic r = 0.557, both *P*<0.0001). The prevalence of sustained hypertension in systolic BP was 27.1% (n = 60). The prevalence of masked hypertension in systolic BP was 25.3% (n = 56). Thus, 52.4% of the patients had systolic hypertension according to the HBP data. On the other hand, the prevalence of diastolic hypertension was lower (24.9%, n = 55).

The average morning BP values were significantly higher than the average evening BP values in all subjects (*P*<0.001 in systolic BP, *P*<0.01 in diastolic BP). The differences between morning
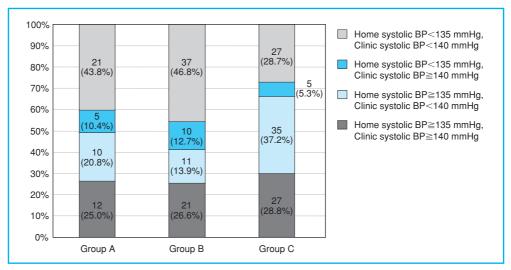
Fig. 2 Percentages of patients' categories according to Home systolic BP and Clinic systolic BP

and evening BP were 4.7 ± 10.8 mmHg in systolic BP and 4.0 ± 6.3 mmHg in diastolic BP.

Achievement of BP control (Table 3)

Table 3 shows the prevalence of each classification according to the recommended BP values (130/80 mmHg). The prevalence of patients who achieved systolic HBP of less than 130 mmHg was 34.8%. The prevalence of patients who achieved diastolic HBP of less than 80 mmHg was 60.2%.

A total of 39.8% of the patients (n = 88) achieved a CBP value of less than 130 mmHg in systolic BP and less than 80 mmHg in diastolic BP. On the other hand, only 25.8% of the patients (n = 57) achieved a HBP value of less than 130 mmHg in systolic BP and less than 80 mmHg in diastolic BP. Of these 57 patients, Group C had a significantly lower prevalence than Group A or B (Group A; 35.4%, Group B; 35.4% and Group C; 12.8%, $P<0.001$ by the chi-square test).

Influence of CKD stage or anemia (Fig. 2)

Group C had a significantly higher prevalence of masked hypertension in systolic BP than Group A and B (37.2%, $P<0.01$ by the chi-square test) (Fig. 2). Although the average systolic HBP in Group C was significantly higher than in Group A and B ($P<0.05$, 0.01) (Table 3), the average systolic CBP was not significantly different. The average diastolic HBP values were not signifi-

cantly different. The mean numbers of antihypertensive drugs were not significantly different among the 3 groups (Group A; 2.0 ± 0.9, Group B; 2.1 ± 0.9, Group C; 2.3 ± 1.0). However, 3 or more antihypertensive drugs and furosemide were more often prescribed to Group C than to Group A or B ($P<0.001$ by the chi-square test).

There was no significant correlation between hematocrit levels and HBP or CBP in each group. Erythropoietin was given to 2 patients in Group B and 37 patients in Group C. Patients receiving erythropoietin treatment had a significantly lower Ccr than those without erythropoietin treatment in Group C. However, there were no significant differences in HBP, CBP and hematocrit levels between these patients groups.

Influence of underlying renal diseases (Table 4, Fig. 3)

The average systolic HBP in the DN patients was significantly higher than that in the nDN patients in each Ccr group (all $P<0.01$) (Table 4). On the other hand, the average systolic CBP was not significantly different in Group A and C. In Group B, systolic CBP was significantly higher in the DN patients than in the nDN patients ($P<0.01$).

The prevalence of masked hypertension or sustained hypertension was higher in Group C than in Group A and B in both the DN patients and the nDN patients (Fig. 3). In addition, the

Table 4 Average BP in each group and comparison between diabetic nephropathy and non-diabetic renal diseases

		All subjects	Diabetic nephropathy (DN)	Non-diabetics renal diseases (nDN)	P DN vs nDN
Home BP (mmHg)					
Group A	Systolic	135.1 ± 16.6	145.4 ± 14.4	131.7 ± 16.0	<0.01
	Diastolic	78.4 ± 10.9	76.8 ± 11.4	79.0 ± 10.8	n.s.
Group B	Systolic	134.1 ± 16.2	141.2 ± 16.3	130.4 ± 14.9	<0.01
	Diastolic	77.4 ± 10.0	76.6 ± 10.9	77.7 ± 9.5	n.s.
Group C	Systolic	141.2 ± 14.7[a,b]	146.5 ± 14.5	137.5 ± 13.8	<0.01
	Diastolic	77.1 ± 10.7	72.9 ± 9.4	80.0 ± 10.7	<0.01
Clinic BP (mmHg)					
Group A	Systolic	129.5 ± 17.4	132.3 ± 16.5	128.6 ± 17.8	n.s.
	Diastolic	70.9 ± 12.5	65.2 ± 11.0	72.9 ± 12.5	n.s.
Group B	Systolic	133.2 ± 19.0	140.1 ± 17.4	129.6 ± 18.9	<0.05
	Diastolic	71.7 ± 12.1	72.9 ± 12.0	71.2 ± 12.1	n.s.
Group C	Systolic	131.3 ± 18.1	134.4 ± 19.5	129.3 ± 16.9	n.s.
	Diastolic	67.6 ± 11.2[c]	63.4 ± 10.2	70.5 ± 11.0	<0.01

a; $P<0.05$ vs Group A, b; $P<0.01$ vs Group B, c; $P<0.05$ vs Group B

prevalence of masked hypertension or sustained hypertension tended to be higher in the DN patients than in the nDN patients in each Ccr group (Group A; $P=0.02$, Group B; $P=0.05$, Group C; $P=0.08$ by the chi-square test).

Assessment of dietary salt intake

The average value of urinary sodium excretion was $151±64$ mEq/day in all subjects, $180±81$ mEq/day in Group A, $155±51$ mEq/day in Group B, and $134±54$ mEq/day in Group C. The frequency of urinary sodium excretion levels of less than 102 mEq/day (equivalent to 6 g/day of sodium chloride) was only 20.8% ($n=46$) in all subjects, 14.6% ($n=7$) in Group A, 16.5% ($n=13$) in Group B, and 27.7% ($n=26$) in Group C.

Discussion

Our results showed that only 40% of the patients controlled their hypertension based on HBP (systolic BP<135 mmHg and diastolic BP<85 mmHg). Although less than 130/80 mmHg in CKD patients is recommended in the current guidelines, the target BP values based on HBP measurement is not clear in these patients. Only 25% of the patients achieved the recommended BP values (systolic BP<130 mmHg and

diastolic BP<80 mmHg). The Ohasama Study and the Japan Home versus Office Blood Pressure Measurement Evaluation (J-HOME) Study showed that only 40% to 55% of treated patients with essential hypertension had been controlled based on HBP, which agrees with our results.[3–5] Target BP should be lower in CKD patients than in the general population or patients with essential hypertension.[2,12] Our results showed that even conventional BP control is insufficient and more aggressive intervention is necessary for BP control in CKD patients.

Our study showed that 71.9% of the patients had controlled diastolic BP (HBP<85 mmHg and CBP<90 mmHg). The Ohasama Study and the J-HOME Study showed that 65% to 72% of treated patients with essential hypertension had been controlled based on D-HBP, which agrees with our results.[3,5] Therefore, both patients with essential hypertension and those with CKD controlled DBP more adequately than SBP. However, it is possible that an increase in pulse pressure due to decreased vascular compliance, rather than the effect of antihypertensive treatment, influences DBP. In CKD patients or in the general population, elevation of systolic BP is an important factor associated with the risk of declining renal function.[15,16] Thus, control of SBP may be more important than control of DBP in
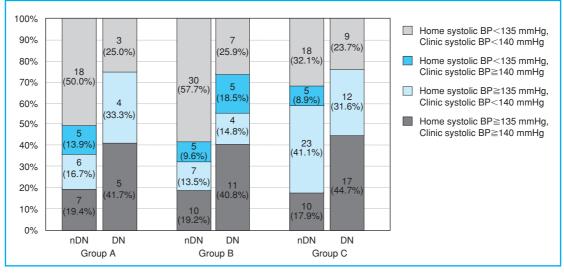
Fig. 3 Percentages of patients' categories according to Home systolic BP and Clinic systolic BP
Comparison between diabetic nephropathy (DN) and non-diabetic renal diseases (nDN)

CKD patients.

Various prevalences of masked hypertension have been reported in previous studies. In recent studies, 9% to 25% of treated general hypertensive patients had masked hypertension based on HBP measurement.[3,4,9] Our results suggest the greater prevalence of masked hypertension in CKD patients than in general hypertensive patients. HBP measurement also plays an important role for CKD patients in detecting insufficient BP control. In addition, our results showed that the prevalence of masked hypertension was significantly greater in patients at an advanced stage of CKD. This indicates that HBP measurement is especially necessary for BP control in these patients. We suggest several reasons for the greater prevalence of masked hypertension in patients at an advanced stage of CKD. First, CKD patients are generally salt-sensitive, and increased salt intake elevates BP.[17] As renal function declines, salt sensitivity tends to increase. In addition, as renal function declines, the fall in nocturnal BP diminishes, resulting in abnormal circadian BP patterns.[18] High morning BP or evening BP may indicate abnormal circadian BP patterns, which is prevalent in patients at an advanced stage of CKD. Furthermore, increased sympathetic activity may influence circadian BP patterns.[19]

We defined the mean values of morning and evening BP as the HBP values. While several studies also adopted the average values of multiple occasions,[9,13] most of the large studies adopted morning BP as the HBP values.[3–5,7] Several studies also indicated higher morning BP values than evening BP values.[6] This tendency was similar to our results. Therefore, it is necessary to consider the differences in the definition of HBP values.

Anemia or erythropoietin treatment has some influence on BP in CKD patients. However, our results showed no significant relationship between these factors and BP.

We compared BP control between patients with DN and those with non-diabetic renal diseases. The significance of BP control is equivalent in patients with both renal diseases. Our results suggest that BP control is more difficult and is controlled more inadequately in patients with DN. A Japanese study showed that morning hypertension with controlled CBP was more common and was related to vascular complications even in patients with DN without renal failure.[20] We suggest that HBP measurement is more necessary to detect uncontrolled BP or improve BP control in patients with DN.

Several current guidelines recommend dietary salt reduction to no more than 6 g per day.[2,12] Our results showed that only 20.8% of the patients excreted sodium of less than 102 mEq/day, which

was equivalent to 6 g of salt. Although many of our patients received dietary counsel from a dietitian, our results showed insufficient adherence to and difficulty in achieving the recommended salt intake in CKD patients. It is necessary to clarify whether dietary salt restriction will reduce masked or sustained hypertension in these patients.

Several studies showed the prognostic significance of HBP in CKD patients.[21–23] Further studies are needed to clarify whether the intervention of BP control based on HBP measurement will improve renal or total mortality.

There are several limitations in our study. First, the devices used in HBP measurement are not uniform. However, all the patients used arm-cuff devices and the accuracy of the devices was checked. We suggest that differences in devices have little influence on the results.

Second, a short rest before BP measurement or single measurement may have some influence on the BP data. Several guidelines recommend at least 5 minutes' rest for BP measurement.[1,2] In addition, repeated measurements are recommended to improve the reliability of measurement.[1,2] The first measurement was reported to be higher than repeated measurements.[24] We could not evaluate the variability of BP. However, a large Japanese study showed that even by a single measurement on each occasion, the average HBP values of multiple occasions have stronger predictive power for stroke risk.[25] Thus, the issue of whether repeated measurements are better than a single measurement on each occasion is not resolved. The Japanese Society of Hypertension permits single measurement on each occasion for HBP measurement.[2] Al-though we adopted the average values of 14 measurements as the HBP value, the CBP value was obtained by a single measurement. A single measurement, especially in the clinic, might give an erroneous classification of hypertension in some patients in this study.

Third, it took a long time to obtain the BP data. Therefore, seasonal variation in BP may influence BP data. Although various seasonal differences in BP were shown in the previous reports, higher BP values tend to be shown in the winter than in the summer.[26]

Finally, the numbers, doses or classes of the antihypertensive drugs or time of administration were not uniform. In addition, the duration of action of the antihypertensive drugs may be different among the drugs. The weakness of the antihypertensive effect might influence the HBP values in some patients. Although our purpose is not to identify the specific effects of or responses to antihypertensive treatment, medication may influence the results.

In conclusion, BP was not adequately controlled in a significant proportion of CKD patients receiving antihypertensive treatment, based on HBP measurement. HBP control was especially insufficient in patients at an advanced stage of CKD and in those with DN. HBP measurement is essential for BP control in CKD patients.

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Lower Urinary Tract Dysfunction in Patients with SMON (subacute myelo-optico-neuropathy)

Tetsuro Konishi,*[1] Isao Araki*[2]

Abstract

The relation between disturbance of activities of daily living and lower urinary tract dysfunction estimated by the International Prostate Symptom Score was examined in 66 patients with subacute myelo-optico-neuropathy (SMON). Forty-three patients (65%) were considered to have symptomatic lower urinary tract dysfunction. Storage urinary symptoms correlated significantly with the severity of gait disturbance in SMON patients, especially in female patients, suggesting that lower urinary tract dysfunction originates in the spinal cord as damage by clioquinol intoxication. In male patients, voiding symptoms also correlated with the Barthel Index and gait disturbance. However, since voiding symptoms tended to be correlated with age in male patients, these symptoms may be associated with age-related development of bladder outlet obstruction, such as benign prostatic hyperplasia.

Key words Clioquinol, Clinical study, Voiding dysfunction, SMON

Introduction

Subacute myelo-optico-neuropathy (SMON) is a disease caused by clioquinol intoxication, characterized by the subacute onset of sensory and motor disturbance in the lower extremities, with visual impairment following abdominal symptoms, mainly occurring during the 1950–60's in Japan.[1,2] The pathological features are characterized by system degeneration of the long tracts of the spinal cord combined with polyneuropathy and optic nerve involvement.[3] After banning the sale of drugs containing clioquinol in September 1970, a sharp decrease in the number of SMON patients was observed in Japan. It is estimated that the number of SMON patients slightly exceeded 3,000 in 2002 and mean age of 1,031 SMON patients exceeded 70 years old (mean age + SD, 72.9 + 9.6) with a female predominance (male: female; 1: 2.75).[4] The mean age of SMON

patients in Japan has constantly increased due to an absence of new patients with SMON.

From a nationwide survey of 419 SMON patients by the SMON Research Committee, the prevalence of urinary incontinence increased from 3.3% always and 34.6% sometimes in 1990 to 6.2% and 54.2%, respectively, in 2000.[5] Urinary complications severely disturb the patient's activities of daily living. Sensory and motor disturbance in SMON may cause some types of neurogenic bladder dysfunction. However, the prevalence of lower urinary tract dysfunction (LUTD) also increases with age. Thus, it is unclear whether LUTD in SMON patients occurs simply due to aging or is related to neural lesions in SMON.

To examine this problem, LUTD in SMON patients was characterized using severity scales and age. The International Prostate Symptom Score (I-PSS) was originally used for quantitative evaluation of subjective lower urinary tract

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symptoms (LUTS) in benign prostatic hyperplasia.[6] Subsequently, this procedure was extended to evaluate LUTS in various conditions in men and women. Since the I-PSS questionnaire includes particular questions on storage and voiding urinary symptoms,[6] both of these types of urinary symptoms can be separately examined. Previous studies by this group indicated that LUTS quantified by I-PSS reflects well the urodynamic abnormalities in central nervous system diseases, such as Parkinson's disease[7,8] and multiple sclerosis.[9]

Materials and Methods

Using I-PSS, lower urinary tract dysfunction (LUTD) was evaluated in 66 patients (17 males, 49 females, ranging from 49 to 96 years of age (mean, 72.2)) with SMON living in Kyoto Prefecture, Japan, in 2000. The duration of SMON disease was $33.2 + 2.4$ years (mean + SD), and the range was 30 to 41 years. Clinical symptoms of SMON were evaluated using medical checkup records established by the SMON Research Committee. Because each questionnaire was answered by the patients themselves or by their relatives without the aid of neurologists or urologists, there may exist some uncertainty of clinical evaluation of SMON patients. In each patient, the total scores for the Barthel Index[10] were calculated. Gait scores were obtained from the severity of gait disturbance. The severity of gait disturbance was classified into 5 grades as follows: bed-ridden, able to move using a wheelchair, able to walk with aid on a flat area, able to walk without aid except up stairs, able to climb stairs without aid. SMON patients with severe complications such as cerebrovascular disease, disease of the peripheral nervous system or dementia were excluded from this study.

The I-PSS questionnaire comprises 7 questions on LUTSs and additional questions on general satisfaction with the urinary condition. Frequency, urgency and nocturia may reflect the state of storage symptoms (maximal score 15), whereas incomplete emptying, intermittency, weak stream and staining at the beginning of urination may be indicative of voiding symptoms (maximal score 20).[6] In addition to these questions, urinary incontinence, sleep condition and desire for therapy for urinary disturbance were included.

Among nonparametric analyses, Spearman's rank correlation coefficients were calculated between variables. All P-values presented are 2-tailed. $P < 0.05$ was considered statistically significant. Multiple regression analyses with forward regression and with backward elimination were conducted to assess the independent association of age, gender, Barthel Index and severity of gait disturbance with the storage or voiding symptom scores. The inclusion or elimination thresholds were $P < 0.05$.

Results

Arbitrarily, patients with a symptom index score of 12 or higher were considered to have symptomatic voiding dysfunction.[7] With this criterion, 43 patients (65%) were found to be symptomatic. When the score for storage symptoms or voiding symptoms was >7 or >9, patients were considered to be symptomatic.[7] Eleven patients (17%) had storage symptoms alone, and 8 patients (12%) had voiding symptoms alone. Twenty-six patients (39%) manifested both types of symptoms.

Urinary incontinence was observed in 18 patients (27%) and sleep disturbance due to frequent nocturia was observed in 34 patients (55%). Fourteen (24%) out of 56 patients wanted medical treatment for their urinary disturbance.

Correlations between the I-PSS score and age, and the Barthel Index score and severity of gait disturbance were examined in all patients and in each sex (Table 1). In all SMON patients, the I-PSS scores significantly correlated with the Barthel Index and gait scores ($P < 0.05$). Each parameter of the Barthel Index was not correlated with the I-PSS score. In female SMON patients, severity of gait disturbance was significantly correlated with the storage symptom scores. The age of female SMON patients was correlated with neither the total scores, the storage scores nor the voiding symptom score. In male SMON patients, the Barthel Index and gait scores were significantly correlated with the total urinary symptom scores, and with the voiding symptom scores. As in female SMON patients, severity of gait disturbance was significantly correlated with the storage symptom scores. The age of male SMON patients tended to be correlated with the total scores and the voiding symptom scores but was not significant.

Table 1 Spearman's rank correlation coefficient between the I-PSS score and age, plus the Barthel Index score and severity of gait disturbance in all patients and in each sex

	Total	Storage	Voiding
All patients (66)			
Age	0.129	0.199	0.024
Barthel Index	− 0.257*	− 0.226	− 0.181
Severity of gait disturbance	− 0.337**	− 0.380**	− 0.172
Female patients (49)			
Age	0.062	0.175	− 0.081
Barthel Index	− 0.141	− 0.176	− 0.044
Severity of gait disturbance	− 0.223	− 0.330*	− 0.028
Male patients (17)			
Age	0.350	0.254	0.367
Barthel Index	− 0.553*	− 0.272	− 0.647**
Severity of gait disturbance	− 0.642**	− 0.497*	− 0.597*

*: $P < 0.05$, **: $P < 0.01$

Multiple regression analyses with forward regression and with backward elimination showed that female and older-age-group patients with low Barthel Index scores under 50 points were important factors influencing the storage symptom score. However, no significant factors that influence the voiding symptom score were clarified.

Discussion

In a nationwide survey of SMON patients in Japan in 2002, complications were present in 93% of 1,032 SMON patients and were mostly geriatric problems, such as cataract, hypertension, vertebral disease, limb articular disease, digestive dysfunction, heart disease and bone fractures.[4] Incontinence of urine was seen in 60.7% and of feces in 32.7%.[4]

Using the I-PSS questionnaire, more than a half the SMON patients (65%) were found to have LUTD, as evaluated by I-PSS. This high percentage was compatible with the percentage complaining of urinary incontinence, obtained from a nationwide survey of SMON patients in Japan in 2000, in which the prevalence of "urinary incontinence sometimes" was 54.2%.[5] From the results of I-PSS applied to SMON patients, storage symptoms correlated with disability of motor function of the lower extremities examined using both nonparametric and mul-

tiple regression analyses, suggesting that storage symptoms in SMON patients are caused by spinal cord lesions from intoxication with clioquinol.[3] Multiple regression analyses suggested that female and older-age-group patients with lower Barthel Index scores were important factors for evaluating the storage symptom scores. The spinal cord origin of LUTD in SMON indicated by our study is compatible with the results of urodynamic studies for 6 patients with SMON, in which supranuclear pelvic nerve dysfunction was suggested to be mainly responsible for the micturitional disturbance.[11] The reported increase in the prevalence of urinary incontinence over the last 10 years[5] may reflect the increase in the mean age of SMON patients, with no new SMON patients reported since 1970. The prevalence of lower urinary tract symptoms in Asian men showed an increase in all symptom scores of IPSS with advancing age.[12] The scores in subjects aged 70 to 79 years were approximately twice those of subjects aged 40 to 49. In male patients, the gait scores significantly correlated with voiding symptoms as well as storage symptoms. However, voiding symptoms showed some correlation with age, suggesting that the urinary symptoms in male patients were caused at least partly by age-related infravesical obstruction (i.e. benign prostatic hyperplasia). The presence or absence of prostatic hypertrophy in male patients was not clear in this study due to a lack

of precise urological investigations. The pathophysiological differences between male and female SMON patients are not clear in this study due to the age factors especially observed in male patients and a lack of precise urodynamic study of each patient. Similar studies during or just after clioquinol intoxication would be useful for clarifying the effects of clioquinol on the autonomic nervous system including urinary functions and sex differences.

Acknowledgements

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Recent Topics in Treatment of Osteoporosis

Satoshi Soen[*1]

Abstract

It has come to light that osteoporosis-related fractures are more critical than previously thought from the perspective of ADL and QOL disorders, and mortality. The goal of osteoporosis treatment is fracture prevention. The diagnosis of osteoporosis is evident by the reduction of bone mineral density. However, in addition to bone mineral density, other important risk factors include bone metabolism markers, preexisting fractures, body weight, genetic predisposition, smoking, falling, and so forth. In the future, overall assessment of these factors will be necessary for starting the treatments. Drug therapy is one of most effective treatment in fracture prevention which increases bone strength. Drugs proven to prevent fractures in all areas of the body are alendronate and risedronate. Hip protectors are also effective to relieve the shock from falls.

Key words   Postmenopausal osteoporosis, Fracture, Bone mineral density, Bone quality, Bisphosphonate, Hip protector

Introduction

Recent advancements in the field of bone metabolism such as osteoporosis are remarkable. In this paper, I would like to describe the definition of osteoporosis, the severity of osteoporosis-related fractures, diagnosis and treatment of primary osteoporosis, mainly focusing on issues after 2000.

What Is Osteoporosis?

First, I would like to discuss what osteoporosis is. In 1993, a WHO consensus group advocated that the "osteoporosis is a systemic skeletal disease characterized by low bone density and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility." At the time, about 80% of bone strength was thought to be defined by bone mineral density. However, today it is widely believed that 50% at most, or under some conditions, only a couple of percent in bone strength is related to bone mineral density. In 2000, a new definition of osteoporosis was advocated in the National Institutes of Health (NIH) consensus statement.[1] According to the NIH, "Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture." Bone strength is thought to be decided by the integration of bone mineral density and bone quality. Bone quality is defined by the ultrastructure of bones, bone turnover, accumulation of micro damages, level of calcification, properties of the bone matrix such as collagen, and so forth.

In Japan, since insurance covers the cost of bone metabolism markers, and the measurement of bone turnover can be easily done in clinical practice, the easiest way of measuring bone quality at the present time is by bone metabolism markers. Historically, postmenopausal osteoporosis was thought to indicate high metabolic turnover, while senile osteoporosis showed low metabolic turnover. However, after the bone metabolism marker came to be used in actual clinical settings, it was found in Japan that in

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many cases of postmenopausal women, even at an advanced age, postmenopausal osteoporosis indicated high metabolic turnover.[2]

The Severity of Osteoporosis-Related Fractures

Osteoporosis-related fractures rank as the second most common underlying cause of being bedridden for those over 65 years of age in Japan. Japan is a long-life country with its high life expectancy. According to the 2002 Japanese abridged life table, the average life expectancy is 78.32 years old for men and 85.23 for women. While the average life expectancy for Japanese men ranks No. 2 in the world, that of Japanese women has been the world's highest for more than 10 years. As the elderly population increases in number, femoral neck fractures, which are the number one contributing factor to being bedridden, will increase. The number exceeded 100,000 per year in 2002.

On the other hand, among osteoporosis-related fractures, vertebral fractures are the highest in frequency. One of the characteristics of this fracture is that only 1/3 of the cases are symptomatic.[3] In most other osteoporosis-related fractures, the majority of the patients visit hospitals with pain caused by injuries. However, in many vertebral fractures, there is no injury or pain. Even without pain, it is proven that as the number of vertebral fractures increases, ADL and QOL disorders deteriorate.[4] In addition, although QOL disorders associated with other osteoporosis-related fractures subside over time, QOL disorders associated with vertebral fractures are known to be difficult to treat effectively. One reason for this is that in spite of the success of treating most non-vertebral fractures without deformities, many successful treatments of vertebral fractures result in remaining deformities.

In addition, the level of QOL disorders associated with these osteoporosis-related fractures are thought to be equivalent to that of rheumatoid arthritis or heart failure and could lead to death.[5] Japanese data show that among those with femoral neck fractures, approximately 13% die within 1 year and about 25% within 2 years. North European data show that the mortality rate of femoral neck fractures per 100,000 to be equal to that of strokes. Osteoporosis as a whole has a 5-year mortality rate, about the same as that of breast cancer and it also has 4 times the mortality rate of uterine cancer, a cause of death in women.

As these facts are revealed, it is clear that osteoporosis and its related fractures are far more critical than previously thought in terms of ADL and QOL disorders, and mortality. As a result, fracture prevention has become the dominant goal in treatment for osteoporosis.

Diagnosis of Primary Osteoporosis

Next, I would like to discuss the diagnosis of primary osteoporosis. Many cases of primary osteoporosis are postmenopausal osteoporosis. In Japan, the Diagnostic Criteria (revised in 2000) by the Japanese Society for Bone and Mineral Research is used for diagnosis (Table 1).[6] Physicians are expected to diagnosis osteoporosis from two conditions.

One is in cases of fragility fractures, which are non-traumatic fractures caused by minor external forces due to low bone mass. Especially, if patients have existing vertebral fractures, the risk of both new vertebral fractures and non-vertebral fractures such as femoral neck fractures increase,[7] and active treatment is needed. On the other hand, as mentioned earlier, since 2/3 of the cases of vertebral fractures exhibit no symptoms, including back pain, and so forth, when vertebral fractures are suspected, a spinal X-ray is necessary. Since X-rays in all cases suspected to be osteoporosis are not possible, if there is evidence or an alternative examination method which point to the existence of vertebral fractures, they would be useful in everyday practice. In the past, a decrease of more than 2 cm of body height from the maximum body height has been used as criteria for diagnosing of vertebral fractures. However, in many cases, patients do not remember their body height, and measuring the arm span is used as a substitute for maximum body height. Recent studies have indicated that both the sensitivity and specificity of this measurement method are not so high. As a result, new examination methods such as the Wall-Occiput Test, or the Rib-Pelvis Distance Test have been found to be effective in both sensitivity and specificity.[8] In the Wall-Occiput Test, patients stand against the wall with heels, hip, and back touching the wall. While keeping the eyes and auricula horizontal with the floor, a

Table 1 Diagnostic criteria for primary osteoporosis (Year 2000 revision)

	Bone mineral density (BMD)	Radiographic osteopenia of the spine
I With fragility fracture		
II Without fragility fracture		
Normal	YAM: more than 80%	Absent
Decreased bone mass	YAM: 70%–80%	Possible
Osteoporosis	YAM: less than 70%	Present

YAM: young adult mean (age, 20–44 years)
Bone mineral density usually refers to lumbar BMD. However, when the measurements is inappropriate for reasons such as spinal deformity, the femoral neck BMD should be used. When measurement at those site is difficult, BMD of the radius, second metacarpal bone, or calcaneus will be used.
(Diagnostic criteria for primary osteoporosis : year 2000 revision[6])

space is created between the wall and the occipital region. With the Rib-Pelvis Distance Test, patients stand with arms extended forward. The distance between the lower end of the ribs and the crest of the ilium becomes less than the breadth of 2 fingers. If the results of these tests are found to be positive, the possibility of vertebral fracture is high. In these cases, X-rays are necessary, and if a vertebral fracture is confirmed, it is diagnosed as osteoporosis.

In cases other than fragility fractures, if the bone mineral density value is less than 70% of the Young Adult Mean (YAM), or if osteoporosis is found in spinal X-ray, osteoporosis is diagnosed. As for bone mineral density measurements, for patients younger than 65 years of age, the diagnostic criteria recommends measuring bone mineral density at the lumbar region of the spine and for patients over 65 years of age, at the femoral neck. In fact, study have shown that when measuring bone mineral density and bone strength of the vertebra, the femur, and the radius from human cadavers, the concordance rate of the results was 50 to 60% at identical sites. At different sites, it was only 20 to 30%.[9] Since the goal of osteoporosis treatment is to prevent fractures, it is necessary to decide which bone of patients' body to target for prevention and to measure the bone mineral density at that site. Based on the incidence rate of fractures by age, for those younger than 65 it seems necessary to prevent the most frequent vertebral fractures. However, for those above 65, the risk of femoral

neck fractures is rising. Since this type of fracture is more critical than vertebral fractures from the standpoint of ADL and QOL disorders, and mortality for those in this age range, it can be said that femoral neck fractures should be prevented. With this background, the setting of bone mineral density measurement sites by age as mentioned earlier is ideal. However, since this type of measurement method is difficult unless using DXA for the entire body, if it is not available, other measurement methods can be used.

Currently, the diagnosis of osteoporosis worldwide is done by measuring bone mineral density. However, a monotonic relation is observed between bone mineral density and the risk of fracture, it seems better to think of this value as merely a cut-off value, not a threshold value. In other words, as the risk of fractures associated with osteoporosis not only decrease in bone mineral density, there are various other factors such as disorders in bone metabolism markers, a history of fractures, body weight, genetic predisposition, smoking, risk of falls, and so forth (Table 2),[10] and ideally it seems desirable to evaluate all these risk factors and decide appropriate treatment to prevent fractures.
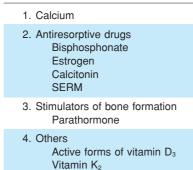
Treatment of Primary Osteoporosis

Lastly, I would like to discuss the treatment of primary osteoporosis. There are several methods to prevent fractures: increase of bone strength, fall prevention, shock absorption when falling.

Table 2 Examples of significant relative risks of hip fractures in women with and without adjustment for BMD

Risk factor	Relative risk	
	Crude	Adjusted for BMD
Hip BMD 1 SD (standard deviation) below mean population value	2.6	
Non-carboxylated osteocalcin above normal range	2.0	1.8
Biochemical index of bone resorption (CTX) above premenopausal range	2.2	2.0
Prior fragility fracture after age 50 years	1.4	1.3
Body weight below 57.8 Kg	1.8	1.4
First-degree relative with a history of fragility fractures and aged 50 years or over	1.7	1.5
Maternal family history of hip fracture	2.0	1.9
Current cigarette smoking	1.9	1.2
Poor visual acuity ($<2/10$)	2.0	2.0
Low gait speed (1 SD decrease)	1.4	1.3
Increase in body sway (1 SD increase)	1.9	1.7

(Prevention and Management of Osteoporosis[10])

Table 3 Classification of drugs used for osteoporosis

1. Calcium

2. Antiresorptive drugs
   Bisphosphonate
   Estrogen
   Calcitonin
   SERM

3. Stimulators of bone formation
   Parathormone

4. Others
   Active forms of vitamin D_3
   Vitamin K_2

Increasing bone strength is done mainly by drug therapy—especially with sufficient calcium and vitamin D supplementation. In this sense, it can be said that dietetic therapy is also important. Exercise therapy is useful for reducing the risk of falls. Although it is confirmed that exercise therapy is effective to prevent falls, its effect on fracture prevention is yet to be confirmed. Hip protectors are effective for absorbing shock during falls, though they are not easy to put on and take off.

The types of fractures to be prevented in the treatment of primary osteoporosis are as mentioned earlier. In postmenopausal women, they are mainly vertebral fractures, while for those above 65 or 70 years of age, they are femoral neck fractures. The purpose of drug therapy was previously pain reduction. Nowadays, with the increase in bone mineral density, it has shifted to improvement of bone strength including the correction of bone metabolic disorders. In clinical trials as well, the effectiveness of prevention against fractures has been investigated.

Drugs used for osteoporosis can be divided into 4 types: 1) calcium, 2) antiresorptive drugs such as bisphosphonates including etidronate, alendronate, and risedronate, calcitonin, estrogen, and selective estrogen receptor modulator such as raloxifene, 3) stimulators of bone formation such as PTH, and 4) other drugs such as active forms of vitamin D_3, and vitamin K_2 (Table 3). Calcitonin, which is available in spray forms, is proven to have antiresorptive effects. However, in Japan, the parenteral form is used, although its effectiveness in fracture prevention is not confirmed. PTH is only approved abroad. Active forms of vitamin D_3 has a bone metabolic modulating effect, while vitamin K_2 stimulates bone formation. Both of these effects are mild compared with antiresorptive drugs and PTH.

According to the WHO Technical Report Series 2003,[10] drugs with the highest evidence

Table 4 Evidence for the efficacy of therapies in osteoporosis

Intervention	BMD	Vertebral fracture	Non-vertebral fracture	Hip fracture
Calcium	A	B	B	D
Calcium + vitamin D	A	—	A	A
Estrogen	A	A	A	A
Tibolone	A	—	—	—
Alendronate	A	A	A	A
Etidronate	A	B	D	D
Risedronate	A	A	A	A
Ibandronate	A	—	—	—
Calcitonin	A	C	C	D
Fluoride	A	C	—	—
Anabolic steroids	A	—	—	D
Calcitriol	C	C	C	—
Alfacalcidol	C	C	—	D
Raloxifene	A	A	—	—
Ipriflavone	B	—	—	—
Menatetrenone	B	B	—	—

Evidence A: positive evidence from one or more, adequately powered, randomized controlled trials; B: positive evidence from smaller non-definitive randomized controlled trials; C: inconsistent results from randomized controlled trials; D: positive results from observational studies; —: efficacy not established or not tested

(Prevention and Management of Osteoporosis[10])

levels for preventing vertebral fractures are as follows: estrogen, alendronate, risedronate, and raloxifene; for preventing non-vertebral fractures and femoral neck fractures, Ca + vitamin D, estrogen, alendronate, and risedronate (Table 4)[10] are recommended. As recent research has shown that the risk of estrogen treatment is greater than its benefits for women,[11] it is used less than other drugs in osteoporosis treatment. Furthermore, although the effectiveness of Ca + vitamin D treatment has been proven in the very elderly, such as those who are in nursing homes, it should be taken into consideration that the results vary. For these reasons, regardless of fracture sites, drugs with proven fracture preventative effects are alendronate and risedronate, while raloxifene is effective only for vertebral fractures.

Both of these drugs have antiresorptive effects. Since postmenopausal osteoporosis indicates high metabolic turnover in many cases, these results seem inevitable. For assessment of the efficacy of these drugs, the use of bone metabolism markers is recommended. Generally, during a period of 3 to 6 months, a reduction of increased metabolic markers can be observed.
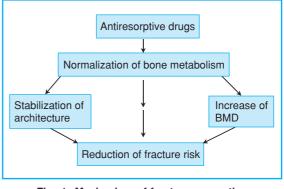

Fig. 1 Mechanism of fracture prevention by antiresorptive drugs

On the other hand, as for bone mineral density, it has been shown that the bone mineral density of the lumbar spine indicates the biggest increase, while that of the proximal femur shows relatively less increase, and it is difficult to see meaningful variation with peripheral DXA or ultrasound.[12] With the limitation in the assessment of efficacy by bone mineral density, measurement using a bone metabolism marker is recommended.

First, antiresorptive drugs correct bone metabolic disorders. With this, architecture is stabilized and bone mineral density is increased. The increase in bone strength has the effect of fracture prevention (Fig. 1).

In addition, at the present time, there is evidence of definite fracture preventative effects for osteoporosis. It can be said that we have no choice but to choose inevitable effective drugs.

As for directions for future research, there is no evidence of fracture preventative effects in combination with drugs. Further research in this field is needed. Furthermore, the issues of osteoporosis among young people are becoming clear. We are now in a decade when we have to consider the necessity of osteoporosis prevention for the younger generation.

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Differential Diagnosis of Pleural Effusions

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Abstract

A variety of disease states are associated with the development of pleural effusions, which sometimes makes the differential diagnosis problematic. Pleural effusions can be classified into two categories, transudative and exudative, based on the characteristics of the pleural fluid. While transudative effusions are the result of changes in hydrostatic or oncotic pressure with no pathological change in the structure of the pleural membrane or condition of the vascular wall, exudative effusions collect in the pleural cavity as a result of pathological changes or structural breakdown of the pleura. In recent years, Light's diagnostic criteria have been most commonly used to differentiate between these two categories of pleural effusion and to help delineate the underlying cause, including malignant tumors, infectious diseases (such as tuberculosis), collagen vascular disease, liver disease, pancreatic disease, iatrogenic causes, and gynecological diseases. Pleural mesothelioma secondary to asbestos exposure has been recognized as a cause of pleural effusion, but diagnostic confirmation is difficult in some cases. When pleural effusion cannot be controlled despite treatment of the underlying cause, pleurodesis can be performed as a potentially permanent method of treatment.

Key words Pleura, Effusion, Transudate, Exudate, Mesothelioma, Thoracentesis

Introduction

A variety of disease states are associated with the development of pleural effusions (Table 1), and depending on the disease, the pleural effusion can either exhibit specific or nonspecific characteristics. A diagnosis of pleural effusion may be suggested by characteristic symptoms (e.g., chest pain, dyspnea) and physical exam findings (e.g., dull lung bases on auscultation and percussion) but definitive diagnosis requires radiological imaging. In particular, X-rays taken with the patient in the decubitus position have high diagnostic sensitivity, and computerized tomography imaging can detect even small amounts of pleural effusion and thus play a significant role in the assessment of intrapulmonary and extrapulmonary lesions. Thoracic ultrasound examination is another effective method of confirming the presence of pleural fluid and determining appropriate access sites for thoracentesis. Because intrapulmonary lesions can go undetected when the pleural effusions are large, CT imaging should be repeated once the fluid has been drained. Further, special attention should be paid to the rate and volume of fluid aspiration during thoracentesis, as rapid or large volume drainage may result in re-expansion pulmonary edema.

Pathophysiology of Pleural Effusions

Pleural fluid is continually secreted by blood capillaries in the visceral and parietal pleural membranes, but most of this fluid is normally secreted from the parietal pleura. Typically, the amount of fluid produced is equal to the amount reabsorbed by the flow of lymph from the visceral pleura. Consequently, the fluid keeps the pleural surface moist and reduces friction between the pleural membranes during respiratory excursion without accumulating in the pleural cavity. This balance between fluid production and absorption

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Table 1 Causes of pleural effusions

Infectious diseases	All pneumonic pleural inflammations, acute empyema, chronic empyema, tuberculosis pleuritis, parasitic infection (lung fluke, etc.)
Malignant tumors	Primary lung cancer, metastatic lung cancer, thymoma (pleural metastasis, pleural seeding), leukemia, Hodgkin's disease, multiple myeloma, malignant pleural mesothelioma
Collagen diseases	Rheumatoid arthritis, SLE, Churg-Strauss syndrome
Gastrointestinal diseases	Liver cirrhosis, acute pancreatitis, liver abscess, subphrenic abscess, peritonitis, esophageal perforation
Cardiovascular diseases	Congestive heart failure, lung infarction, ruptured thoracic aortic aneurysm, Dressler syndrome
Renal disease	Nephrotic syndrome
Gynecological diseases	Meigs syndrome, pleural endometriosis
Iatrogenic diseases	Drugs, post-thoracic/abdominal surgery complications, radiation
Other	External injury, spontaneous pneumothorax, benign asbestos pleurisy, sarcoidosis, yellow nail syndrome, pulmonary lymphangiomyomatosis

Table 2 Light's criteria

1. Ratio of pleural fluid protein to total serum protein is 0.5 or more.

2. Ratio of pleural fluid LDH to total serum LDH is 0.6 or more.

3. Pleural fluid LDH is two-thirds or more of the upper limit for serum LDH.

is maintained through multiple forces, including plasma osmolality, hydrostatic pressure, venous pressure, and capillary wall permeability.

A transudate results from fluid that accumulates in the pleural cavity as a result of a breakdown in the balance between pleural fluid production and absorption in the context of a normal pleural membrane, vascular wall, and lymphatic vessel structure. For example, in some cases pleural fluid accumulates as a result of an increase in fluid production due to increases in hydrostatic pressure, reductions in oncotic pressure, or reductions in absorption. By contrast, an exudate results from fluid that accumulates in the pleural cavity as a result of structural breakdown or increased vascular permeability. In such cases, further tests are often necessary to determine the underlying cause of this pathologic phenomenon.[1]

Characteristics of Pleural Fluid

The characteristics of pleural fluid differ according to the underlying pathological condition but can be broadly classified into two categories, transudative and exudative, and then further into subcategories, such as purulent, bloody, and chylous, according to appearance and smell. Although the classic Rivalta reaction can also be of assistance, Light's diagnostic criteria (Table 2) are most commonly used to differentiate between transudative and exudative effusions. According to this method, an exudative effusion is diagnosed if one or more of three criteria are satisfied. When the pleural effusion is diagnosed as exudate by this criterion in spite of clinically being considered as transudate, the difference of albumin concentration between serum and effusion is greater than 1.2 mg/dl, then the effusion is diagnosed as transudate. The amount of LDH present in the pleural fluid is a rough indicator of the extent of pleural inflammation and is useful in assessing treatment outcomes. Transudative pleural fluid is often present in both sides of the chest and is caused by heart failure, nephrotic syndrome, low-protein leukemia, malnutrition, hypothyroidism, and other systemic diseases.[2]

Since the condition often resolves with treatment of the underlying cause or with diuretics, thoracentesis is typically not required unless there is ventilatory impairment or significant mediastinal displacement.

Diagnosis of Exudative Effusions

In 25% of cases, pleural effusion result from malignant disease. In another 20–40% of cases, biochemical testing, bacteriological examination, and pathological cytology of the pleural fluid fail to identify any underlying cause of disease. In such cases, either cytology is repeated or a pleural biopsy is performed.

Malignant tumors

With malignant tumors, the pleural effusion is often bloody, but ordinary exudative pleural effusion is also possible. Malignant effusion can result from primary cancer of the lungs, pleural mesothelioma, leukemia, lymphoma, or metastatic spread of other tumors to the lung.

The sensitivity of a single pleural fluid cytology examination ranges from 40–80%; thus, in the case of a negative result, the test should be repeated. Pleural effusion is usually unilateral in distribution but can also be bilateral if effusion spreads to the contra lateral pleural membrane. Pleural fluid CEA and other tumor markers are useful diagnostic adjuncts. When there is no tumor detected in the lungs, metastasis from other organs is suspected, and evaluation of the stomach, pancreas, large intestine, ovaries, and breasts should be conducted to identify occult tumors. Indeed, in patients with a history of breast cancer, the disease can recur and manifest with pleural effusions more than 10 years after the original cancer has been ostensibly cured. In other cases in which adenocarcinoma cells are found in the pleural fluid without the identification of any primary tumor, the condition is often designated as carcinomatous pleurisy resulting from primary lung cancer.

Approximately 30–80% of patients with pleural mesothelioma also have pleural effusions, less than half of which are bloody. In such cases, cytological diagnosis is difficult, and detection of elevated levels of pleural fluid hyaluronic acid, which are caused by the accumulation of large amounts of hyaluronic acid in mesothelial cells, may be necessary for correct diagnosis. Measurement of serum mesothelin-related protein (SMRP) also has high specificity for a diagnosis of pleural mesothelioma, but only a limited number of facilities in Japan are able to perform this procedure.

Infectious diseases

Tuberculous pleural effusion is straw-colored fluid contains fibrin and comprises approximately 70% lymphocytes. The incidence of tuberculous bacilli positive culture from pleural fluid cultures is up to 20%, and the data of PCR testing is various results. A pleural ADA of greater than 50 IU/L is suggestive of tuberculosis, but pleural ADA can also be elevated in the context of thoracic empyema, RA, and Hodgkin's disease. Pleural fluid IFNγ levels may also be elevated in the context of tuberculosis, but determination of IFNγ levels is seldom performed.

Parapneumonic effusions secondary to bacterial pneumonia typically resolve with treatment of the underlying pneumonia. However, a foul-smelling purulent pleural fluid containing a large amount of neutrophil cells (e.g., thoracic empyema) may also develop. Diagnostic evaluation of the pleural fluid in patients with empyema typically reveals high numbers of white blood cells, high LDH, low glucose, and sometimes isolation of bacteria. In cases in which the pleural fluid pH $<$ 7.0, drainage of the pleural cavity is necessary, and pleural lavage is performed if purulence is strong. Causative microorganisms include *Pneumococcus pneumoniae*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *E. coli*, *Streptococcusmilleri group*, *Mycoplasma pneumoniae*, and anaerobic bacterias such as *bacteroides*. *Nocardia, Actinomyses* species, fungi, and parasitic infections, such as *Paragonimus miyazaki*, *Paragonimus westermani*, and *Echinococcus* are also with pulmonary effusions. Parasitic pleural effusion often contains large amount of eosinophils.

Collagen diseases

Rheumatoid arthritis and SLE can also cause exudative effusions. RA with pleural effusion is more frequently in man than in woman in spite of strong predilection of arthritis for woman. Pleural effusions may sometimes be the initial presenting manifestation of RA. In patients with RA, pleural effusions are characterized by a low blood glucose concentration ($<$ 30 mg/dl) in more than 78% of cases due to changes in pleural

membrane permeability. Also, LDH tends to be high, pH tends to be slightly low, and complements, especially C4, are reduced to less than 4 mg/dl.[3]

In SLE, pleural effusion can manifest as aseptic meningitis, pericarditis, and peritonitis. Common symptoms include fever, abdominal pain, and peritoneal signs, which can be confused with a diagnosis of diffuse peritonitis and result in exploratory laparotomy. In patients with SLE, the pleural fluid is often positive for antinuclear antibodies and lupus erythematosus cell. Further, in patients with Churg-Strauss syndrome, the pleural fluid may be rich in eosinophils.

Gastrointestinal diseases

In patients with liver cirrhosis, ascites passes through the diaphragm (e.g., a transudate) and accumulates in the right side of the chest. In cases of subphrenic abscesses, exudative fluid accumulates in the pleural cavity. With pancreatitis, the pleural fluid usually accumulates in the left side of the chest, but cases of fluid accumulating in the right side or both sides have been reported. S-amylase rises if the effusion has been caused by esophageal perforation or rupture. Amylase is also elevated in approximately 10% of malignant pleural effusions.[4]

Chylous pleural effusion

Chylous pleural effusion is suspected when the pleural fluid is opaque and milky white, with a fatty supernatant even after centrifugation. Further, the opacity disappears when the pleural fluid is mixed with ether. Chylous pleural effusion is caused by lymph seeping into the pleural cavity following damage to thoracic ducts as a result of lymphangioleiomyomatosis (LAM), mediastinal lymphoma, external injury, or surgery. A change in diet to low-fat foods can be expected to slow the rate of accumulation and slightly reduce the amount of accumulated fluid.

Other

Sarcoidosis, Wegener's granulomatosis, eosinophilic pneumonia, and iatrogenic pneumonia can also cause fluid to accumulate in the pleural cavity. Benign asbestos pleurisy is diagnosed in cases in which there is a history of exposure to asbestos and in which no other plausible cause for the exudative effusion can be found. This diagnosis requires the absence of a malignant tumor for three years after the pleurisy diagnosis.

When no diagnosis can be made despite assessments of pleural fluid characteristics, cytology, bacteriological testing, or other forms of examination, a pleural biopsy is performed. Although the procedure is performed under local anesthesia using a needle designed especially for this purpose, it is not uncommon for the biopsy to find little more than nonspecific pleural inflammation. In such cases, thoracoscopic lung biopsy can be performed to achieve a definite diagnosis.

Treatment

Treatment of the underlying disease is the principle treatment for pleural effusions. Emergency procedures are required when there is a large amount of fluid, when breathing has been impaired, when cardiac function has been compromised, or when pleural bleeding resulting from external injury cannot be controlled. Drainage of the pleural space should also be instituted promptly in cases of acute thoracic empyema.

Small pleural effusions caused by malignant tumors will sometimes resolve with chemotherapy, but pleurosclerosis is performed after the fluid has been drained in cases where effusion reoccurs or when more that a moderate amount of effusion is present. If pleurodesis is performed on both sides, ventilatory function may decreases and consequently QOL may worsen. So this procedure is usually performed on only one side in Japan.

Drainage of the pleural cavity

The skin and pleura are sufficiently anesthetized, and a catheter is inserted into the pleural cavity. Atropine sulfate can be administered intramuscularly as a preanesthetic medication to prevent vagal reflex. A double-lumen tube may be easier to use when pleural lavage or chemical dosing is planned. Blood pressure may drop, and re-expansion pulmonary edema may occur if drainage is too fast; thus for elderly patients in particular, drainage should be kept to a maximum speed of 1,000 ml/hr and 1,000–2,000 ml/day. When using a large catheter to ensure that no air enters the pleural cavity when the catheter is inserted, it is important that careful attention is paid to the drainage speed, as 1,000–2,000 ml can quickly gush out as the catheter is being secured and connected. As the pleural fluid drains out

and decreases and the lungs expand, the patient should be warned that the procedure will likely provoke coughing. Vital signs should be checked during and after drainage to ensure that general condition is stable.

Pleurodesis

After the pleural effusion is thoroughly drained, medication is injected into the pleural cavity. A drainage tube is clamped securely to enable the medication to flow uniformly for 4–6 hours. After this period, the clamp is released. The tube is removed once drainage has dropped to less than 100 ml per day. This procedure sometimes ends in failure when pulmonary atelectasis occurs or when air enters the pleural cavity. The medication generally used in the case of pleural adhesions is picibanil, but minomycin and the chemotherapy drugs, cisplatin, adriamycin, and mitomycin, are also used.

Pleural lavage

When thoracic empyema is diagnosed, the pleural fluid must be drained. In such cases, pleural lavage is also performed to prevent irregular pleural adhesions and large-scale pleural thickening. After a sufficient amount of pleural fluid has been removed using as thick a catheter as possible, approximately 1,000 ml of sterile normal saline is injected and then drained. This is repeated several times until CRP and other inflammation observations improve. When pleural lavage does not go smoothly due to adhesion of the pleural membranes, one possible solution is to inject 120,000–240,000 units of urokinase, but this treatment is not covered by health insurance. If medical therapy is deemed to have limitations, surgical procedures should be used.

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Head Subcutaneous Metastasis of Endocrine Cell Carcinoma in the Rectum

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Abstract

A 46-year-old man who presented with rectal bleeding was diagnosed with rectal carcinoma. As the tumor was found within 2 cm of the anal verge, he underwent abdmino-perineal resection in November, 2001. The invasive front of the tumor was within the wall of the rectum without serosal invasion. The surgical specimen was diagnosed as endocrine cell carcinoma and one regional lymph node metastasis was revealed located near the tumor. After discharge, the patient underwent adjuvant chemotherapy consisting of p.o. 5-fluorouracil 200 mg/day for more than 6 months. He noticed a head subcutaneous tumor in May, 2002. In June, two more tumors appeared. The tumors were removed surgically under local anesthesia. The surgical specimens were diagnosed as endocrine cell carcinoma, and were judged to be metastasis from the rectal lesion, based on the histological similarity. Cutaneous metastasis of rectal adenocarcinoma is a rare event occurring in fewer than 4% of all patients with rectal cancer. Cutaneous metastasis of endocrine cell carcinoma in the rectum is extremely rare. Furthermore, to our knowledge, no head subcutaneous metastasis of endocrine cell carcinoma in the rectum has been reported to date

Key words Endocrine cell carcinoma, Head subcutaneous metastasis irinotecan

Introduction

In the recently released World Health Organization classification of gastroenteropancreatic (GEP) endocrine tumor,[1] poorly differentiated endocrine carcinomas (PDECs) constitutes a distinct category separate from the other two main categories (i.e. well-differentiated endocrine tumors and well-differentiated endocrine carcinomas) because of the distinctive histological features and highly aggressive clinical behavior with poor prognosis.[2] However it is extremely unusual to detect head subcutaneous metastasis from a rectal lesion even if the case is in the terminal stage. In this report we describe a case of PDEC of the rectum of which the first recurrence lesion was his head subcutaneous, with a relatively long interval between the appearance of subcutaneous metastasis and death.

Case Report

A 46-year-old man who presented with rectal bleeding was diagnosed with rectal carcinoma. As his tumor was found within 2 cm of the anal verge, he underwent abdmino-perineal resection in November, 2001 (Fig. 1). The invasive front of the tumor was within the wall of the rectum without serosal invasion. The surgical specimen was diagnosed as endocrine cell carcinoma by pathological examination including grimelius and neuron specific enolase (NSE) immunolabeling

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of the histological features (Fig. 2A, B, C) and revealed one regional lymph node metastasis located near the tumor. Ki 67 immunolabeling of the histological features showed that the tumor was low grade malignancy (Fig. 2D).

After discharge, he underwent adjuvant che-

Fig. 1 Surgical specimen
The 4-cm diameter tumor is located in the lower rectum.

motherapy consisting of p.o. 5-fluorouracil 200 mg /day for more than 6 months. He noticed a head subcutaneous tumor in May, 2002. In June, two more appeared (Fig. 3). The tumors were removed surgically under local anesthesia. The surgical specimens were diagnosed as endocrine cell carcinoma by pathological examination including grimelius and neuron specific enolase (NSE) immunolabeling of the histological features (Fig. 4A, B, C), and were judged to be metastasis from rectal lesions, based on the histological similarity. Ki 67 immunolabeling of histological features showed that the metastatic lesions were high-grade malignancy (Fig. 4D). We performed computed tomography (CT) and radioisotope examination, but no other was detected. In addition, the blood serotonin level was within normal limits.

Therefore, 5-fluorouracil was not an effective agent for his disease. He underwent systemic chemotherapy consisting of irinotecan (CPT-11) $80 \, mg/m^2$ every 2 weeks from August, 2002. However, we confirmed multiple spreading to the lungs by CT in February, 2004. In addition,
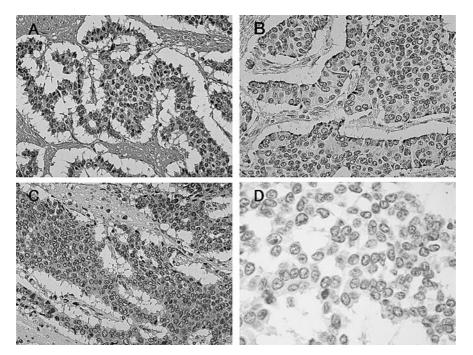

Fig. 2 Pathological finding of the primary tumor
A: Histological features of the tumor (H&E, ×200)
B: Grimelius immunolabeling of histological features (×200)
C: Neuron specific enolase (NSE) immunolabeling of histological features (×200)
D: Ki 67 immunolabeling of histological features (×400)

cervical spine metastasis was diagnosed by radioisotope examination. He died in September, 2004, which is more than 24 months after systemic chemotherapy was initiated, and approximately 36 months after the first operation was performed.
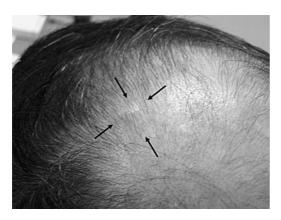

Fig. 3 Head subcutaneous metastasis
Arrows point out three tumors about 1-cm in diameter in the head area.

Discussion

Cutaneous metastasis of rectal adenocarcinoma is a rare event occurring in fewer than 4% of all patients with rectal cancer.[3] While metastasis can be found in any location of the cutaneous, rectal cancer most often metastasizes to the middle or lower dermis of the abdomen and the perianal skin, usually to the abdominal wall and around the umbilicus; the metastasis also often appear after surgery for rectal carcinoma.[4,5]

On the other hand, endocrine cell carcinoma most often metastasizes to liver and systemic lymph nodes. Cutaneous metastasis of endocrine cell carcinoma in the rectum is extremely rare. Furthermore, to our knowledge, no cases of head subcutaneous metastasis of endocrine cell carcinoma in the rectum have been reported.

As to Ki 67 immunolabeling of histological features, the primary lesion was low-grade malignancy, but the metastatic lesions were high-grade malignancy. In our patient, there was no relationship between the grade of malignancy in
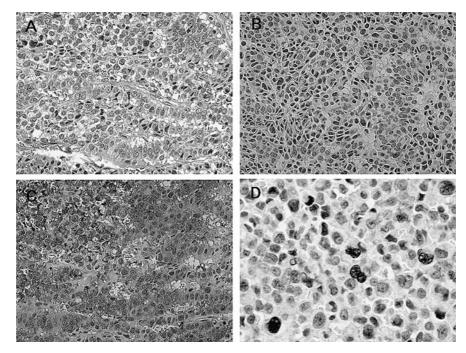

Fig. 4 Pathological finding of the metastatic lesion
A: Histological features of the tumor (H&E, ×200)
B: Grimelius immunolabeling of histological features (×200)
C: Neuron specific enolase (NSE) immunolabeling of histological features (×200)
D: Ki 67 immunolabeling of histological features (×400)

the primary lesion and the occurrence of distant metastasis.

With regard to adjuvant chemotherapy for endocrine cell carcinoma, some reports state that 5-fluorouracil is an effective agent for liver metastasis.[6] However our adjuvant chemotherapy consisted of 5-fluorouracil 200 mg/day perosly, head subcutaneous metastasis occurred within 1 year after the first operation. No other effective chemotherapeutic drugs for endocrine cell carcinoma have been reported. However, there was one report that irinotecan is an effective agent for pulmonary small-cell carcinoma.[7] Therefore, we administered irinotecan after removing the head lesions.

Survival after diagnosis of skin metastasis ranges from 1 to 34 months,[8,9] Our patient survived for more than 24 months from diagnosis of subcutaneous metastasis to death, which is a relatively long survival following diagnosis of subcutaneous metastasis. Although irinotecan might be useful as chemotherapy for endocrine cell carcinoma, we have no evidence to support this.

As to the metastatic route to head subcutaneous, it may be either by hematogenous or lymphovascular spread.

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Central Nervous System Relapse after Autologous Peripheral Blood Stem Cell Transplantation in Primary Plasma Cell Leukemia

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Abstract

The usefulness of autologous stem cell transplantation (auto-SCT) has not been established for primary plasma cell leukemia (PCL). After achieving complete remission with chemotherapy, a 61-year-old man underwent autologous peripheral blood stem cell transplantation with a conditioning regimen comprising melphalan 200 mg/m^2 in December 2002. He was discharged on Day 26 in complete remission. PCL relapsed in cerebrospinal fluid 3 months after transplantation. Intra- and extra-thecal plasmacytomas also developed, but no bone marrow relapse was documented. The patient died of disease progression on Day 236 after auto-SCT. Novel therapeutic approaches to PCL are needed.

Key words   Melphalan, t(11;14), VAD therapy, Autologous stem cell transplantation,
                 Primary plasma cell leukemia

Introduction

Plasma cell leukemia (PCL) is a rare variant of multiple myeloma (MM).[1,2] This disease is defined by circulating plasma cells >2,000/mm^2 and plasmacytosis accounting for >20% of the white blood cell count (WBC). Primary PCL is defined as plasma cell proliferation first diagnosed in the leukemia phase, and reportedly displays a poor prognosis.[1,2] Autologous stem cell transplantation (auto-SCT) is an optimal therapy for MM. In primary PCL, only a small case series has been reported, and the clinical outcome has not been well described.[3–5] We report herein the case of a patient with primary PCL who developed central nervous system (CNS) relapse after auto-SCT.

Case Report

A 61-year-old man was referred to Toyohashi Municipal Hospital in May 2002 due to leukocytosis. He complained of forearm pain but did not display fever, skin eruptions or lymphadenopathy. Survey radiography or scintigraphy did not detect any bone lesions. Computed tomography revealed mild hepatosplenomegaly. Laboratory examination revealed the following results: hemoglobin, 13.8 g/dl; platelet count, 8.3×10/μL; WBC, 30,550/μL with 10% peroxidase-negative atypical cells; serum LDH, 653 IU/L; total protein, 6.0 g/dL; and Bence-Jones type-l protein. Bone marrow examination revealed infiltration with 55% atypical cells (Fig. 1). Atypical cells were positive for CD38, CD126 and p53 and negative for CD56 on immunopathological examination of a bone marrow clot. Primary PCL

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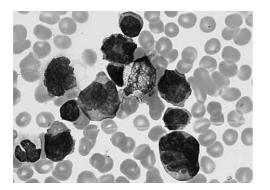
**Fig. 1   Atypical cells in bone marrow
(May-Giemsa stain × 400)**

**Fig. 2   Intra- and extrathecal plasmacytoma
(magnetic resonance imaging)**

T1-weighted image after gadolinium enhancement showing hyperintensities along the cauda equina (short arrow). There is an intrathecal mass-like lesion (arrow). The vertebral mass considered to be plasmacytoma is apparent at the level of L3 (arrowhead).

was diagnosed. Cytogenetic analysis revealed a complex karyotype including 43, X, $-$ Y, der(1;22) (q10;q10), dup(1)(q21q32), add(5)(d11), del(6)(q?), $-10, -13,$ add(13)(p11), add(15)(p11), $-16, +$ mar1, $+$ mar2. Fluorescent in situ hybridization analysis revealed translocation (11;14) and deletion of 13q14 (RB1) and 17p13 (p53).

Complete remission was achieved after 3 courses of ROAD[6] (vincristine 1.2 mg/mm^2 × 1 day; ranimustine 40 mg/mm^2 × 1 day, melphalan 8 mg/mm^2 × 6 days, dexamethasone 40 mg × 4 days) and 4 courses of VAD therapy (vincristine 0.4 mg/mm^2 × 4 days, doxorubicin × 4 days, dexamethasone 40 mg × 12 days). After successful peripheral blood stem cell collection, the patient underwent autologous peripheral blood stem cell transplantation (auto-PBSCT) with a conditioning regimen comprising melphalan 200 mg/m^2 in December 2002. Neutrophil engraftment was achieved on Day 10, and he was discharged on Day 26 in complete remission.

Lumbago developed 3 months after auto-PBSCT. Magnetic resonance imaging (MRI) revealed intra- and extrathecal plasmacytomas at the L3 level (Fig. 2). Cerebrospinal fluid (CSF) examination revealed 8,448/mm^3 atypical plasma cells, whereas bone marrow examination revealed a normal distribution of cells and serum, and urine M-protein or Bence-Jones protein were not detected in the serum or urine. Intrathecal administration of 15 mg methotrexate and 4 mg dexamethasone was initiated. Atypical plasma cells disappeared after 5 courses of intrathecal administration into CSF. Extrathecal plasmacytomas were treated supportively

without chemo- or radiotherapy. The patient did not receive additional intrathecal chemotherapy due to pancytopenia.

The patient complained of lumbago three weeks after the last intrathecal administration, and atypical plasma cells in CSF increased. He died of disease progression on Day 236 after auto-SCT.

Discussion

This case indicates that patients with primary PCL could develop CNS relapse and that physicians must be careful in watching for the development of neurological symptoms after auto-SCT. CNS involvement in patients with MM is uncommon.[7] Auto-SCT has become a therapeutic option in MM, although reports of CNS relapse after auto-SCT are limited.[8] Patients with primary PCL are more likely to develop extramedullary involvement.[3] Although we must take into consideration the fact that we only used as a conditioning regimen high-dose melphalan, which fails to penetrate the blood brain barrier into CSF, the frequency of CNS relapse after auto-SCT might be higher in primary PCL than

in MM. There is another concern that the procedure of auto-SCT might induce the risk of CNS involvement. However, information on the association between auto-SCT and CNS involvement is highly limited in MM or PCL. Further investigations are warranted.

The efficacy of auto-SCT for primary PCL has not been established. Our patients relapsed soon after auto-PBSCT. According to the data of The International Bone Marrow Transplant Registry, 2 of 5 patients with PCL died of disease progression within 1 year after auto-SCT.[3] This indicates that auto-SCT has insufficient antitumor effect against primary PCL. Additional novel agents, such as thalidomide or bortezomib, intrathecal chemotherapy before and after auto-SCT and allogeneic SCT might be worth investigating. Further studies are warranted.

The establishment of risk strategies against primary PCL is required. Cytogenetic abnormalities might be useful for identifying high-risk patients with primary PCL, as in MM. Our patient displayed deletion 17q13 and common cytogenetic abnormalities in primary PCL t(11;14), monosomy 13 and abnormality of 1q.[9,10] Although abnormality of t(11;14) is reportedly associated with favorable outcomes,[9] most abnormalities in our patients are unfavorable.[11] Patients with primary PCL display a more complex karyotype than those with MM.[12] This is adifficulty in identifying high-risk patients using cytogenetic abnormalities in primary PCL. Further large-scale studies would allow proper interpretation.

In summary, we presented a case involving CNS relapse after auto-SCT in a patient with PCL. PCL displays clinically different characteristics from MM. Novel therapeutic approaches to PCL need to be established.

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Clinical Topics

Drug-Induced Liver Injury by Dietary Supplements in Japan

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Key words   Drug-induced liver injury, Dietary supplement, Health food, Herbal medicine

Recently, cases of drug-induced liver injury (DILI) by dietary supplements including so-called health foods and herbal medicines have increased in Japan. Much attention has been paid to DILI by dietary supplements since the reports of many cases of severe liver injury by Chinese dietary supplements in July 2002. The increased use of dietary supplements due to a health boom derived from the increase in patients with lifestyle-related illness and doctors' knowledge of DILI by dietary supplements seems to have increased the reports of such cases. In this review, the present status of DILI by dietary supplements in Japan is discussed.

The first nationwide survey of DILI by dietary supplements was reported at the 33rd West Regional Meeting of the Japan Society of Hepatology in 1999.[1] A questionnaire on DILI was sent to active members of the society, and twelve cases of DILI by dietary supplements were included in 2,561 DILI cases between 1989 and 1998. In this survey, DILI by dietary supplements accounted for only 0.5% of total DILI cases. The mean age was 52 years, and 50% were women.[1]

After the reports of DILI cases by Chinese dietary supplements, the Japan Society of Hepatology surveyed DILI cases by dietary supplements.[2] Thirty-one cases of DILI by dietary supplements during 2002 were identified. The mean age was 44 years (24–73 years), and 29 cases (94%) were women. In this survey, most cases (21 cases) were DILI by Chinese dietary supplements. The mean duration until the onset in all cases was 78 days (10–450 days), and that in cases by Chinese dietary supplements was 83 days (11–450 days). Types of liver injury were 23 cases with acute hepatitis, 4 cases with severe hepatitis, 1 case with acute fulminant hepatitis, 1 case with sub-acute fulminant hepatitis, and 2 cases of late-onset hepatic failure. One case of death and 3 cases who received living donor liver transplantation were all due to Chinese dietary supplements.[2]

At a workshop for DILI held in Digestive Disease Week-Japan 2004, Professor M. Onji and I had a chance to survey DILI cases by dietary supplements.[3] In this study, DILI cases by Chinese dietary supplements were excluded. A questionnaire was sent to 14 speakers of the workshop, and 89 cases of DILI caused by dietary supplements were obtained. Figure 1 shows the distribution of age of the patients (mean age was 56 years) and 74% were women. Seventy-one cases (80%) had basal diseases, which consisted of liver diseases (27 cases), endocrine and metabolic diseases (10 cases), malignant tumors (9 cases) and cardiovascular diseases (7 cases). Seventy-one causal supplements were reported; 29 cases by Ukon (Curcuma), 9 cases by Agaricus, 2 cases by Life-pack, Kin-kei-gan, Propolis, So-Chu-Cha, Protein, Fukodain, Ao-jiru, Rei-shi Mushroom (Ganoderma Lucidum), Royal jelly and Russian Chaga, respectively.[3] The most popular aim of the use of dietary supplements was for health (54 cases), followed by that for basal diseases (23 cases). Twenty-three cases were using more than

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Correspondence to: Hajime Takikawa MD, Department of Medicine, Teikyo University School of Medicine, 2-11-1 Kaga, Itabashi, Tokyo 173-8605, Japan. Tel: 81-3-3964-1211, Fax: 81-3-3964-8477, E-mail: takikawa@med.teikyo-u.ac.jp
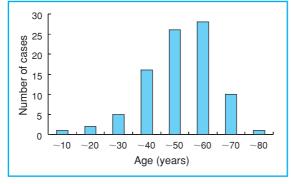
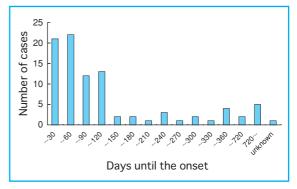Fig. 1 Age distribution of drug-induced liver injury cases by dietary supplements[3]

Fig. 2 Duration until the onset of liver injury by dietary supplements[3]

1 supplement simultaneously, and 53 cases were taking supplements together with approved drugs. Symptoms were observed in 58 cases; 40 cases with general fatigue, 17 cases with jaundice, 9 cases with appetite loss, 9 cases with nausea and vomiting, 8 cases with itching, 7 cases with fever, and 3 cases with eruption or urticaria.[3]

As for the type of liver injury, hepatocellular injury type was the most popular (67 cases), followed by cholestatic type (13 cases) and mixed type (9 cases).[3] The percentage of hepatocellular injury type was higher than that by approved drugs. Seventy cases presented with acute hepatitis, fulminant hepatitis occurred in 3 cases, and one case each of severe hepatitis and late onset of hepatic failure was observed. Figure 2 shows the duration until the onset of liver injury (162 days on average), which was much longer than that by approved drugs.[3] Most patients (56 cases) recovered without special therapies after stopping the use of supplements. Three cases with fulminant hepatitis were subjected to plasma exchange, and one case received living donor liver transplantation. Two cases died due to liver injury; one by fulminant hepatitis considered to be due to Russian Chaga, and the other by multiple organ failure after acute hepatitis due to Ukon.[3]

DILI is classified into toxic and idiosyncratic types. Most DILI cases are the idiosyncratic type, which is further classified into allergic type and metabolic idiosyncratic type. It is yet unknown which type of DILI is common in DILI caused by dietary supplements, but the metabolic idiosyncratic type seems to be popular, since most cases are acute hepatitis type and the durations until the onset of liver injury are relatively long. However, until the characteristics of DILI by dietary supplements are clarified, this question remains unresolved.

DILI by dietary supplements is also a social problem in foreign countries.[4] Recently, 3 sister cases of DILI by usnic acid, which often causes DILI in the United States, were reported from Taiwan.[5] They acquired usnic acid from their relatives living in California.[5] As observed in this example, it is very difficult to estimate how many people are taking such dietary supplements, because we can easily import them privately through the Internet.

The incidence of DILI by dietary supplements is considered to be lower than that by approved drugs, and there are two subjects which have to be resolved in the future. One is surveys for the actual situation of DILI by dietary supplements in Japan. In the United States, 40 million people are consuming at least one kind of supplement per week.[6] However, the frequency of DILI by dietary supplements is not clear even in the United States. According to a recent report from Oregon University, 10 out of 20 patients who received liver transplantation due to fulminant liver failure had recently used dietary supplements.[7] We have to know both the denominator of the people using dietary supplements and the numerator of patients with DILI by dietary supplements in order to calculate the incidence. Therefore, surveys of the numbers of people taking dietary supplements are important. Such information in Japan is very limited. Through a questionnaire to patients with digestive diseases who came to Kurume University Hospital and

related hospitals, 326 patients were using dietary supplements.[8] Popular supplements were vitamins (42%), Ukon (35%), Agaricus (16%) and garlic (13%).[8] Similarly, by a questionnaire to 349 patients with urologic cancer who came to Kurahashi Central Hospital, 164 patients (47%) had used dietary supplements.[9] Popular supplements were Agaricus (52 cases), vitamins (35

cases), Propolis (21 cases) and Ukon (16 cases).[9]

Another important subject is to enlighten people to the fact that even dietary supplements may cause liver injury just as approved drugs do, and to consult doctors for the treatment and prevention of diseases without easy dependence on dietary supplements.

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Recent Progress in Sentinel Node Navigation Surgery

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Key words Sentinel lymph node, Navigation surgery, Minimally invasive surgery, Individulized treatment, Breast cancer, Gastric cancer

The sentinel node (SN), also called the sentinel lymph node, is the first node to receive lymphatic drainage from primary tumors. Sentinel node navigation is a method to identify the SNs and determine operative procedures according to the status and distribution of SNs. If the concept that lymph node metastasis first appears in SN is valid, lymph node dissection can be avoided with no evidence of metastasis in SNs even in cases of significant metastatic risk. Although the SN concept has been investigated since the early 20th century, clinical applications have been realized only after a tracer method and appropriate assistive equipment have been developed. The method, along with gamma probing, utilizes dye-guided and radioisotope injections near the tumors to identify the SNs on the direct drainage pathway. The SN concept attracted attention in clinical settings after Dr. Donald Morton and his colleagues of John Wayne Cancer Institute (JWCI) in the United States reported its significance in the treatment of melanoma in 1992.[1] Multi-center prospective trials incorporating several thousand cases in the United States and Europe on the application of the SN concept to breast cancer have been completed, registered, and are now in the follow-up stage. In the surgical treatment of breast cancer, breast-conserving surgery has recently become widely used. The prevalence of sentinel node navigation biopsy has lead to avoiding unnecessary axillary lymph node dissection.[2] The United States,

Europe, and Japan have applied this method to breast cancer treatment in clinical settings without waiting for the results of large-scale clinical trials. However, since sentinel node navigation surgery is not currently covered under the national health insurance system, each facility is treating the cases as clinical studies so that research budgets may cover the expenses. Since this method has already been widely used in clinical practice, it is necessary that appropriate medical treatment fees be immediately brought under the health insurance umbrella. In order to accomplish this goal, the Japan Society of Sentinel Node Navigation Surgery has established a multi-center cooperative database of sentinel node navigation surgery for breast cancer cases in Japan, with more than 1,400 cases currently registered. This society is also planning to revise the original Japanese evidence-based guidelines on sentinel node biopsy in breast cancer.

Recent single-institutional studies have reported on the application of the sentinel node concept to other solid tumors such as gastrointestinal carcinoma. U.S. and European studies on colon cancer and Japanese studies on gastric cancer are assessing the method in multi-center cooperative studies, raising the expectation for the clinical application of individualized treatment and minimally invasive surgery in gastrointestinal carcinoma treatment.

Research in the United States and Europe has advanced the idea of the sentinel node as an

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index in the accurate diagnosis of lymph node metastasis of colon cancer, and has used the results to advocate the application of adjuvant chemotherapy. In general, since there are many patients in the U. S. and in Europe with abdominal subcutaneous fat and fewer lymph nodes for pathological examination, diagnosis of metastasis using the sentinel node as an index is also useful from a medical economic perspective.[3]

Among gastrointestinal carcinoma, the application of the method for individualized and minimally invasive surgery for gastric cancer holds the greatest promise.[4] The past 5 years has seen an increase in presentations at various academic conferences on SN navigation in gastric cancer and has attracted vast attention. For patients with negative SN metastasis, laparoscopic surgery is feasible as a curative treatment. This trend is unique to Japan, which has a high frequency of early gastric cancer detection. Currently, this method is attracting attention in Asian countries such as Korea, which has a high frequency of gastric cancer. Limited laparoscopic surgery for node negative cases is the most practical treatment for gastric cancer due to anatomical characteristics. Theoretically, patients with gastric cancer with negative SN, to which local excision can be applied, can be cured by laparoscopic local excision of the gastric tumor. With additional research and technological improvement, the clinical significance of SN navigation in individualized early gastric cancer treatment will increase.

Research indicates that the sentinel node concept is valid for esophageal cancer cases diagnosed as cT1 and T2N0.[5] However, since SNs are multiple and are distributed widely in the esophagus, treatment requires gathering a sample of the nodes through excision. Thus, even for cases with negative SN metastasis, it is currently difficult to implement non-invasive surgery. However, identifying the SN basin as the primary region for dissection may contribute to consider the additional dissection of the cervical lymph node, according to SN status. Sentinel node navigation is also useful for selecting a surgical approach (transthoracic or transhiatal) in carcinoma of esophagogastric junction including Barrett's adenocarcinoma, which is increasing in the U.S. and in Europe. Current research has shown the treatment effect of chemoradiotherapy for cT1N0 esophageal cancer with risk of lymph node micrometastases. Even when micrometastases for cT1N0 esophageal cancer are present, there is a high probability that the metastasis is confined to the sentinel node. It is possible to use scintigraphy as another method in determining the radiation field, including the sentinel node.

Therefore, clinical studies investigating the SN concept for diagnosis and treatment of a variety of cancers such as head and neck cancer, thyroid cancer, cervical cancer, prostate cancer, and lung cancer are progressing. Although the technical details and clinical applications vary depending on the characteristics of each organ, common efficacy is observed in individualized treatment based on accurate diagnosis of lymph node status.

Recent observations of the importance of the SN in lymph node cancer metastasis have been made. For example, a factor produced by cancer cells inhibits the functions of macrophage or dendritic cells, which are immunocompetent cells in the SNs, thus promoting metastasis. Furthermore, a lymphangiogenetic factor, produced by cancer-specific cells, reaches the SNs by lymph drainage and there promotes lymphangiogenesis and metastasis. These observations not only clarify the mechanism of metastasis, but also are useful in developing new treatment methods targeting the SNs.

The keywords in cancer treatments in the 21st century are minimally invasive surgery and individualized treatment. There is great hope that SN navigation could become one of the effective methods to accomplish these goals. High quality clinical trials are necessary to demonstrate the legitimacy of this theory in various organs.

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