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Cancer and Pulmonary Embolism
— Thrombotic Embolism, Tumor Embolism, and Tumor Invasion Into a Large Vein —

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Background The specific incidence of thrombotic pulmonary embolism (PE), tumor PE and tumor invasion into large veins according to tumor type and tumor site remains unclear.
Methods and Results A total of 65,181 cancer patients were identified from 98,736 postmortem examinations. Thrombotic PE occurred in 2.32% of all cancer patients and comprised 88.6% of the total number of all PE events. The incidence of thrombotic PE was high in those with adenocarcinoma, leukemia and large cell carcinoma, and was low in those with hepatic cell carcinoma. The incidence of PE was high when tumor was present in hematogenous tissue, lungs, ovaries, pancreas and the biliary system, and was low when tumor was present in the liver. The incidence of tumor PE was high with large cell carcinoma, hepatic cell carcinoma and adenocarcinoma, and was also high when tumor was present in the lungs, ovaries, kidneys and liver. There was a significant correlation between the incidence of tumor PE and the incidence of tumor invasion into large veins.
Conclusion The incidence of thrombotic PE, tumor PE and tumor invasion into large veins varies significantly according to tumor histopathology and tumor site. (*Circ J* 2006; **70:** 744–749)

Key Words: Adenocarcinoma; Autopsy; Hepatic cell carcinoma; Leukemia; Pancreas

Cancer is a major risk factors for thrombotic pulmonary embolism (PE),[1–4] and thrombotic PE associated with cancer is known as Trousseau's syndrome. Cancer induces not only thrombotic PE but also tumor PE and tumor invasion into large veins. However, there is lack of epidemiological data from the general population to compare the incidence of thrombotic PE, tumor PE and tumor invasion to large veins according to the histopathology and the site of the cancer. Clinicians have given more attention to the prevention of venous thromboembolism (VTE) with chemotherapeutic and surgical treatment of cancer patients, but it is important to evaluate the risk of the development of VTE according to the histopathology and primary site of the cancer.

The goal of this study was to investigate variations in the incidence of thrombotic PE, tumor PE and tumor invasion into large veins according to tumor histopathology and tumor site.

Methods

A total of 65,181 cancer patients (66.0%) were identified from 98,736 postmortem examinations.[5–7] The incidence of PE, as well as the tumor site and the histopathology, was recorded for each case. PE was defined as critical (critical PE) when it was the primary cause of death or main diagnosis, and "total PE" was used to indicate the total number of thrombotic PEs, tumor PEs, bacterial PEs, mycotic PEs and other emboli (eg, fat, amniotic fluid etc). The type of emboli was determined by the pathologist performing the autopsy. Cases with 2 different types of emboli were counted twice. All cases were also reviewed for the presence of tumor invasion into a large vein. Within each PE group, the incidence of PE was compared between specific tumor types (adenocarcinoma, mucinous carcinoma, transi-

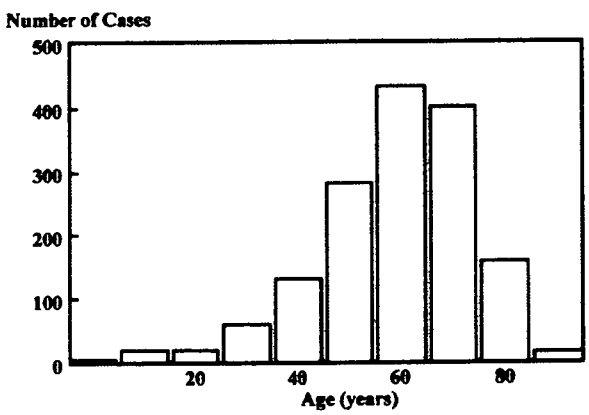

Fig 1. Age distribution of all cases with pulmonary embolism.

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Table 1 Incidence of Pulmonary Embolism (PE) for Each Tumor Type

Tumor type	Total cases	Total PE	Critical PE	Thrombotic PE	Tumor PE	Tumor invasion into a large vein
Malignant lymphoma	3,463	80 (2.31; 1.80–2.82)	22 (0.64; 0.37–0.90)	73 (2.11; 1.62–2.59)	2 (0.06; 0.00–0.14)	0 (0.00; –)
Myeloma	1,030	33 (3.20; 2.11–4.30)	10 (0.97; 0.37–1.57)	31 (3.01; 1.95–4.07)	2 (0.19; 0.00–0.46)	0 (0.00; –)
Adenocarcinoma	23,535	858 (3.65; 3.40–3.89)	253 (1.07; 0.94–1.21)	788 (3.35; 3.11–3.58)	54 (0.23; 0.15–0.26)	18 (0.08; 0.04–0.11)
Leukemia	3,782	178 (4.71; 4.02–5.40)	59 (1.56; 1.16–1.96)	144 (3.81; 3.19–4.43)	2 (0.05; 0.00–0.13)	0 (0.00; –)
Transitional cell carcinoma	1,294	27 (2.09; 1.30–2.87)	18 (1.39; 0.75–2.03)	25 (1.93; 1.17–2.69)	2 (0.16; 0.00–0.37)	0 (0.00; –)
Squamous cell carcinoma	7,055	155 (2.20; 1.85–2.54)	34 (0.48; 0.32–0.64)	144 (2.04; 1.71–2.37)	5 (0.07; 0.01–0.13)	7 (0.10; 0.03–0.17)
Hepatic cell carcinoma	7,971	81 (1.02; 0.79–1.24)	18 (0.23; 0.12–0.33)	52 (0.65; 0.48–0.83)	26 (0.33; 0.20–0.45)	31 (0.39; 0.25–0.53)
Small cell carcinoma	1,846	49 (2.65; 1.91–3.40)	15 (0.81; 0.40–1.22)	46 (2.49; 1.77–3.21)	1 (0.05; 0.00–0.16)	1 (0.05; 0.00–0.16)
Micinous carcinoma	1,412	47 (3.33; 2.38–4.28)	18 (1.27; 0.69–1.86)	43 (3.05; 2.14–3.96)	3 (0.21; 0.00–0.45)	0 (0.00; –)
Large cell carcinoma	714	33 (4.62; 3.04–6.20)	7 (0.98; 0.25–1.71)	29 (4.06; 2.58–5.54)	4 (0.56; 0.01–1.11)	1 (0.14; 0.00–0.41)
p value		<0.0001	<0.0001	<0.0001	0.0008	<0.0001

Data are number (%; 95% confidence interval) of patients.

Table 2 Incidence of Pulmonary Embolism (PE) According to Tumor Site

Tumor site	Total cases	Total PE	Critical PE	Thrombotic PE	Tumor PE	Tumor invasion into a large vein
Liver	9,355	106 (1.13; 0.92–1.35)	22 (0.24; 0.14–0.33)	72 (0.77; 0.59–0.95)	32 (0.34; 0.22–0.46)	35 (0.37; 0.25–0.50)
Breast	1,480	43 (2.91; 2.04–3.77)	17 (1.15; 0.60–1.69)	38 (2.57; 1.75–3.38)	2 (0.14; 0.00–0.32)	0 (0.00; –)
Thyroid	1,781	54 (3.03; 2.22–3.84)	25 (1.40; 0.85–1.95)	50 (2.81; 2.03–3.59)	2 (0.11; 0.00–0.27)	0 (0.00; –)
Hematogenous tissue	4,944	223 (4.51; 3.92–5.10)	72 (1.46; 1.12–1.79)	184 (3.72; 3.18–4.26)	3 (0.06; 0.00–0.13)	0 (0.00; –)
Brain	1,199	20 (1.67; 0.94–2.40)	7 (0.58; 0.15–1.02)	21 (1.75; 1.00–2.50)	0 (0.00; –)	0 (0.00; –)
Lung	10,180	352 (3.46; 3.10–3.82)	84 (0.83; 0.65–1.00)	330 (3.24; 2.89–3.59)	16 (0.16; 0.08–0.23)	4 (0.04; 0.00–0.08)
Uterus	1,318	42 (3.19; 2.22–4.15)	17 (1.29; 0.68–1.90)	40 (3.03; 2.09–3.98)	1 (0.08; 0.00–0.22)	3 (0.23; 0.00–0.49)
Digective system	16,440	447 (2.72; 2.47–2.97)	144 (0.88; 0.73–1.02)	402 (2.45; 2.21–2.68)	33 (0.20; 0.13–0.27)	9 (0.06; 0.02–0.09)
Ovary	835	48 (5.75; 4.14–7.37)	15 (1.80; 0.89–2.71)	45 (5.39; 3.81–6.96)	4 (0.48; 0.01–0.95)	2 (0.24; 0.00–0.57)
Kidney	1,488	32 (2.15; 1.41–2.90)	15 (1.01; 0.50–1.52)	27 (1.81; 1.13–2.50)	7 (0.47; 0.12–0.82)	8 (0.54; 0.17–0.91)
Prostate	2,290	63 (2.75; 2.07–3.43)	28 (1.22; 0.77–1.68)	59 (2.58; 1.92–3.23)	2 (0.09; 0.00–0.21)	2 (0.09; 0.00–0.21)
Biliary system	2,330	89 (3.82; 3.03–4.61)	19 (0.82; 0.45–1.18)	81 (3.48; 2.72–4.23)	1 (0.04; 0.00–0.13)	4 (0.17; 0.00–0.34)
Urinary bladder	1,086	23 (2.12; 1.25–2.98)	8 (0.74; 0.23–1.25)	21 (1.93; 1.11–2.76)	2 (0.18; 0.00–0.44)	0 (0.00; –)
Pancreas	3,445	124 (3.60; 2.97–4.23)	25 (0.73; 0.44–1.01)	118 (3.43; 2.81–4.04)	6 (0.18; 0.03–0.31)	0 (0.00; –)
p value		<0.0001	<0.0001	<0.0001	0.0012	<0.0001

Data are number (%; 95% confidence interval) of patients.

tional cell carcinoma, squamous cell carcinoma, small cell carcinoma, large cell carcinoma, hepatic cell carcinoma, malignant lymphoma, myeloma and leukemia) and sites (lung, digestive system, liver, pancreas, biliary system, hematogenous tissue, kidney, urinary bladder, prostate, breast, uterus, ovary, thyroid and brain).

Statistical Analysis

Statistical analysis was performed using StatView 5.0 (SAS Institute Inc, Cary, NC, USA). Comparisons of the incidence of PE according to tumor type and site were performed using the chi-square test. Data are presented as means with the 95% confidence interval (CI).

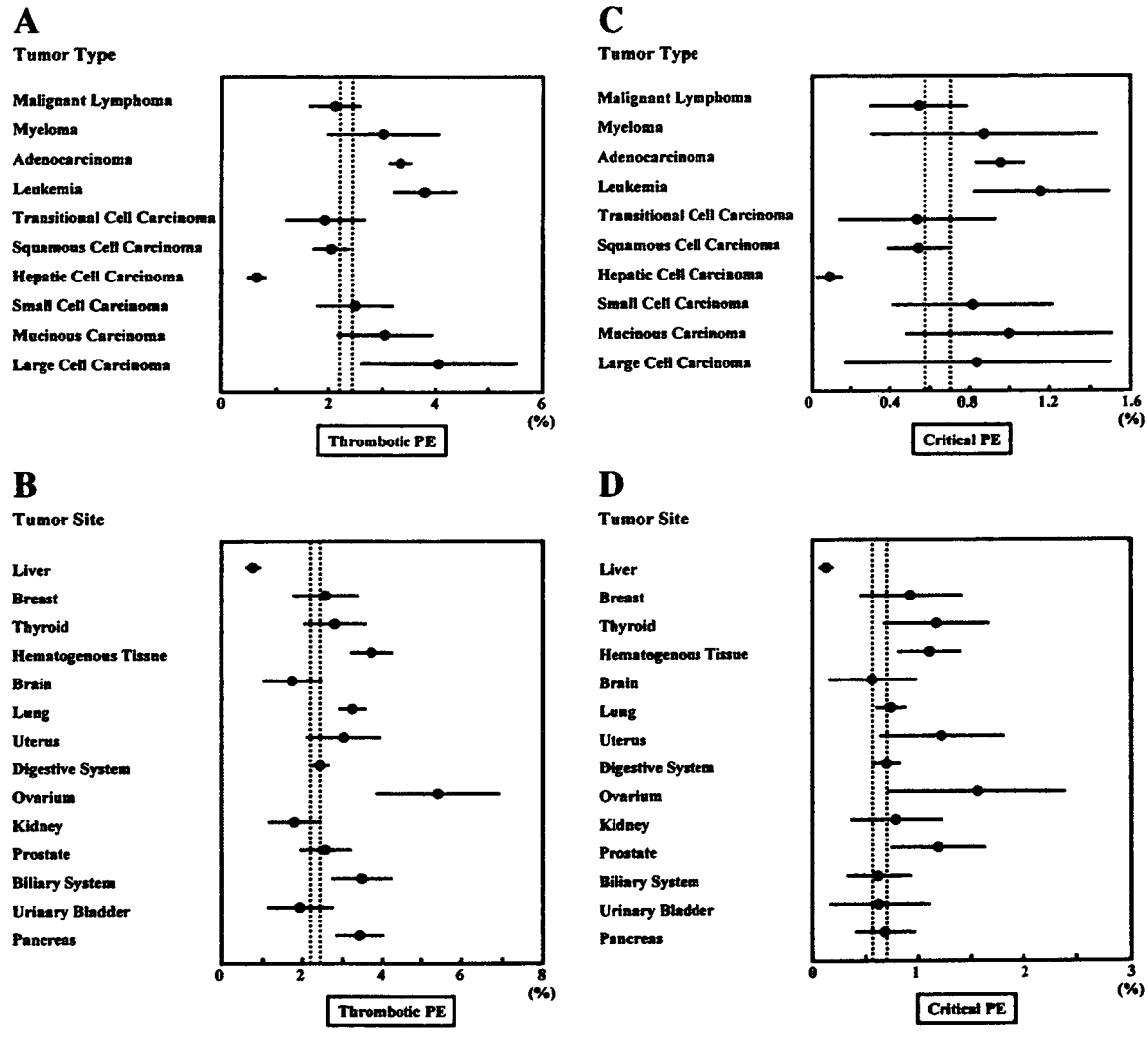

Fig 2. Incidence of thrombotic pulmonary embolism (PE) and critical PE. (A) Incidence of thrombotic PE according to tumor type, (B) incidence of thrombotic PE according to tumor site, (C) incidence of critical PE according to tumor type, and (D) incidence of critical PE according to tumor site. Data are mean and 95% confidence interval (CI). (---) 95% CI of all patients with cancer.

Results

A total of 1,708 patients with any type of PE were identified (2.62%; 95%CI, 2.50–2.74). The age distribution of this population is illustrated in Fig 1, with the peak incidence between ages 60 and 80 years.

The incidence of total PE was significantly associated with tumor site and histopathology (both, $p<0.0001$). Many cases of total PE occurred in patients with adenocarcinoma, leukemia and squamous cell carcinoma among the tumor types (digestive system and lung among the tumor sites) (Tables 1,2). The incidence of PE was high in leukemia, large cell carcinoma and adenocarcinoma (ovary, hematogenous tissue, biliary system, pancreas and lung among the sites), and low in hepatic cell carcinoma (liver and brain among the sites) (Tables 1,2, Figs 1,2). Critical PE was found in 493 patients (0.76%; 95%CI 0.69–0.82), which comprised 28.9% of the total number of PE (493/1,708). Many cases of critical PE occurred with adenocarcinoma, among the tumor types, and in digestive system, lung and hematogenous tissue among the tumor sites. The incidence of critical PE was significantly associated with tumor type and site ($p<0.0001$). The incidence of critical PE was particularly high in leukemia and adenocarcinoma (ovary, hematogenous tissue and thyroid among the tumor sites), and less so in hepatic cell carcinoma and squamous cell carcinoma (liver among the tumor sites).

Thrombotic PE was identified in 1,514 patients (2.32%; 95% CI 2.21–2.44). The incidence was high in large cell carcinoma, leukemia and adenocarcinoma (ovarium, hematogenous tissue, biliary system, pancreas and lung among the tumor sites), and low in hepatic cell carcinoma (liver among the tumor sites).

Tumor PE was identified in 124 patients (0.19%; 95% CI 0.16–0.22) and was particularly frequent in those with adenocarcinoma and hepatic cell carcinoma or when tumor was present in the digestive system and the liver.

Tumor invasion into a large vein was identified in 69 patients (0.11%; 0.08–0.13). The incidence of this complication was high in those with hepatic cell carcinoma and when tumor was present in the liver and kidney. Nine of these 69 patients also had concomitant tumor PE.

Based on 10 histopathologic types of cancer, there was no significant correlation between the incidence of thrombotic PE and the incidence of tumor PE (r=0.21, p=0.57) or between the incidence of tumor PE and the incidence of tumor invasion into a large vein (r=0.51, p=0.13). Based on 14 primary sites of cancer, there was no correlation between the incidence of thrombotic PE and the incidence of tumor PE (r=0.06, p=0.83), but there was a significant correlation between the incidence of tumor PE and the incidence of tumor invasion into a large vein (r=0.71, p=0.004; Fig 3).

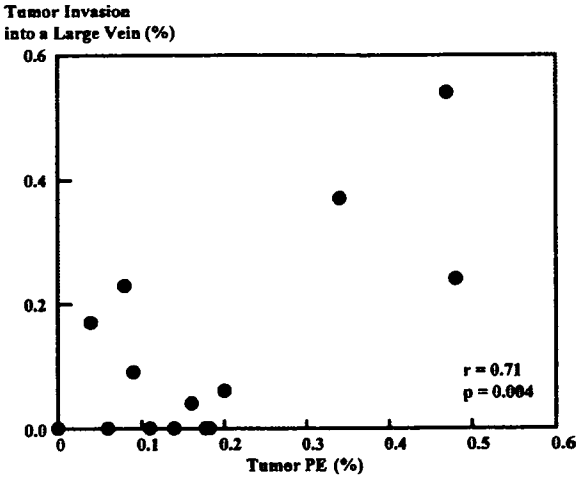

Fig 3. Correlation between incidence of tumor embolism (PE) and the incidence of tumor invasion into a large vein according to tumor site (●).

Discussion

Cancer and Thrombotic PE

In the present study, thrombotic PE was identified in 1,514 (2.32%) of 65,181 cancer patients, and thrombotic PE comprised 88.6% of all PE, including thrombotic PE, tumor PE, bacterial PE, mycotic PE and other emboli (eg, fat, amniotic fluid etc). This is consistent with widely reported data that cancer is associated with a hypercoagulable state that increases the risk of thromboembolic disease[1–4] Furthermore, the use of anticancer drugs can increase the risk of PE[8–10] Previous studies have reported an overall incidence of PE in cancer patients of 1–15%[11] Coon et al reported that 17.1% of 1,394 patients with malignant conditions had thrombotic PE at autopsy[12] which is higher than the incidence of thrombotic PE in the present study. In another clinical study of 1,041 cancer patients, 81 patients (7.8%) were diagnosed with VTE, and the independent risk factors for PE included chemotherapy, advanced tumor, renal cell carcinoma, pancreatic carcinoma, gastric cancer and brain tumor[13] Because the incidence of PE is lower in non-black non-white Americans than in blacks or whites[14–17] the difference in the incidence of PE between these studies may be attributed to racial differences.

In the present study, PE was frequent in patients with adenocarcinoma and when tumor was present in the digestive system, lung and hematogenous tissue. Although malignant tumor is a risk factor for PE, it has been controversial whether we should aggressively investigate for malignant tumor in cases of primary PE. Sorensen et al concluded that aggressive investigation into malignant tumor was not warranted[18]

Relationship Between Thrombotic PE, Tumor Histopathology and Tumor Site

The present study demonstrated that the incidence of thrombotic PE correlated with the tumor type and site. The incidence of thrombotic PE was high for adenocarcinoma, leukemia and large cell carcinoma, and low for hepatic cell carcinoma. Among the sites the incidence was high in hematogenous tissue, lung, ovary, biliary system and pancreas, and low in liver. Spoul et al previously reported the venous thrombosis was associated with carcinoma of the pancreas, particularly if the pancreatic body or tail was involved[19] but there are relatively few reports of venous thrombosis in patients in patients with carcinoma of the liver, which may reflect the high rate of concomitant cirrhosis in these patients, resulting in decreased prothrombin production[19] Indeed, one epidemiological study reported that liver disease reduces the odds ratio of PE[20]

Uderzo et al reported that 12 (2.7%) of 452 children with leukemia had PE and univariate analysis demonstrated a significant correlation between PE and acute myeloid leukemia[21] Furthermore, in a study of 719 adult patients with leukemia (534 acute myelogenous leukemia, 185 acute lymphoblastic leukemia), 15 patients (2.1%, of whom 5 patients had PE) had VTE, and VTE was found in all subtypes of acute leukemia, especially in patients with promyelocytic leukemia, a subtype of acute myelogenous leukemia[22] Finally, Kwaan et al reported that apoptotic acute promyelocytic leukemia cells produce higher levels of thrombin, which increases the risk of hypercooagulability and disseminated intravascular coagulation[23] These results are consistent with our result that PE is frequent in patients with leukemia.

The presence of a mucin-secreting adenocarcinoma of the digestive system and ovaries is also considered as a risk factor for secondary VTE[24] However, in the present study, this relationship did not reach statistical significance, possibly because of the low number of cases with mucinous carcinoma.

Tumor Embolism

In the present study, the incidence of tumor PE also correlated with tumor type and site. The incidence was higher for large cell carcinoma, hepatic cell carcinoma and adenocarcinoma among the tumor types, and higher in lung, ovary, kidney and liver among the tumor sites. Tumor PE and/or tumor invasion into a large vein was present in 193 patients (0.30%), which is less than that reported in previous studies[24,25] For example, the previous studies have reported that 2.4–26% of patients with solid malignant tumors had tumor embolization[25,26] Other studies have demonstrated that the risk of tumor embolization is increased by chemotherapy, radiation and surgical extirpation of the primary tumor, probably because these therapies promote fragmentation of the tumor mass and theoretically enhance tumor embolization via venous or lymphatic drainage[26]

Tumor PE can be classified into 2 different types according to the involvement of specific areas of the pulmonary vasculature. The first type involves either the main pulmonary arteries or the large segmental arteries. This type of emboli often can be diagnosed by pulmonary angiography, computed tomography or magnetic resonance angiography and is typically visible on gross examination at autopsy as

a macroscopic pulmonary tumor embolism. To distinguish tumor PE in proximal arteries from chronic thromboembolic pulmonary hypertension (CTEPH) is important because many cases of CTEPH have the indication of surgical therapy. The differentiation is, however, difficult before surgery or autopsy. The second type of tumor emboli involves the small arteries and/or arterioles, and is often difficult to diagnose correctly and may be considered as pulmonary hypertension of unknown cause antemortem. These microscopic pulmonary tumor embolism may be invisible on gross examination at autopsy. In the present study both of types were included.

Tamura et al reported that major tumor PE was present in 12 (3.8%) of 318 cancer patients at autopsy, including 6 patients with hepatic cell carcinoma and 3 patients with gastric cancer (adenocarcinoma)?[27] Moreover, macroscopic pulmonary tumor embolism was found in 6 patients, all of whom had hepatic cell carcinoma. Further, Ito et al reported that tumor PE was present in 18 patients (3.6%) of 500 cancer patients at autopsy, including 6 patients with sarcoma, 6 patients with hepatic cell carcinomas and 3 patients with renal cell carcinomas?[28] In combination with results from the present study, these data suggest that tumor embolism occurs frequently with hepatic cell carcinoma.

On the other hand, Bassiri et al reported that in 30% of patients with tumor PE the primary site of the cancer was the breast, with lung cancer representing 9% and the prostate 7%?[29] However, in their study the number of the patients according to the type of cancer was unknown, so the incidence of PE was not described. In most studies the described tumor PE has been limited to microscopic pulmonary tumor embolism, so we can not compare our data with those previously reported. Chan et al reported that hepatic cell carcinoma was the major cause of fatal tumor PE in oriental countries?[30] but it is necessary to analyze this issue further.

Tumor Invasion Into a Large Vein

In the present study, the incidence of tumor invasion into a large vein was relatively high when there was tumor present in the liver or kidney. Furthermore, there was a significant correlation between the incidence of tumor PE and the incidence of tumor invasion into a large vein. This is consistent with the observation by Winterbauer et al that patients with hepatic cell carcinoma and major hepatic vein and inferior vena cava invasion had an increased incidence of tumor PE, and that in patients with renal cell carcinoma, tumor emboli were more frequent when the primary tumor invaded the renal vein and inferior vena cava?[26] Moreover, according to their study, they noted that, despite a proclivity for major venous invasion 3-fold that seen in primary carcinoma of the liver, the incidence of tumor embolization was lower in patients with renal cell carcinoma than in those with hepatic cell carcinoma, suggesting that some factor related to tumor integrity or cohesiveness was operating in addition to the pattern of venous invasion in determining the incidence of tumor emboli?[26]

Study Limitations

The first limitation of the present study is that it was based on previously published postmortem examinations. The affected site in the pulmonary vasculature was described in few patients with tumor PE. Therefore, we could not indicate the separate incidences of macroscopic and microscopic tumor PE. The second limitation is associated with the classification of the type of PE. Some cases had more than 1 type of PE (eg, thrombotic, tumor, septic etc). In cases in which 2 types of emboli were present, the patient was counted twice.

Conclusion

Thrombotic PE was found in 2.32% of all cancer patients at autopsy, which is a lower incidence than that found in previous studies. Furthermore, thrombotic PE comprised 88.6% of all cases of PE, including thrombotic PE, tumor PE, bacterial PE, mycotic PE and other emboli (eg, fat, amniotic fluid etc). Finally, the incidence of thrombotic PE, tumor PE and tumor invasion into a large vein was dependent on tumor type and site.

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Acute Pulmonary Embolism after an Earthquake in Japan

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ABSTRACT

There have been no reports on acute pulmonary embolism (APE) after earthquakes. Our aim was to clarify the actual the occurrence of APE following the 2004 Mid Niigata Prefecture earthquake in Japan, and to assess the risk factors for APE after the event. We sent questionnaires to 122 hospitals in the Niigata Prefecture after the earthquake. Cities, towns, and villages in the prefecture were classified into two areas (high evacuee rate area, and low evacuee rate area) due to the mean ratio of evacuees to the overall population during 1 week immediately after the earthquake. A rate of 5% and higher was encountered for the high evacuee rate area and a rate of < 5% was encountered for the low evacuee rate area. Ten out-of-hospital cases of APE (seven in the high evacuee rate area and three in the low evacuee rate area) were diagnosed within the first month after the earthquake. The relative risk of APE was high in the high evacuee rate area (13.09; $p = 0.0002$) and also higher in women (8.55; $p = 0.04$). All patients in the high evacuee rate area had stayed in their automobiles for long periods of time, but none had done so in the low evacuee rate area ($p = 0.008$).

KEYWORDS: Pulmonary embolism, earthquake, gender, economy-class syndrome

Prolonged sitting was shown for the first time to be a risk for acute pulmonary embolism (APE) in a study published during World War II. Venous thromboembolism (VTE) occurred in air-raid shelters in persons who were sleeping in a chair but not when they were sleeping in a bunk.[1] Thereafter, VTEs were reported after long automobile drives and in theaters.[2] More recently, the so-called long-flight syndrome (also known as the economy-class syndrome [i.e., VTE during flights lasting long periods of time]) has been described.[3–7] Lower limb venous compression ultrasonography revealed that there are many asymptomatic VTE cases after long flights.[5,8]

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After a large earthquake, the number of rest rooms in temporary public shelters was inadequate, there was a shortage of portable water, and many people spent long periods sitting in automobiles because of a risk for collapse of houses. Therefore, the risk for VTE may have been elevated. Although earthquake-induced heart attacks have been documented,[9,10] there have been no reports to date on APE after earthquakes.

In this study, we attempted to identify the number of patients with APE that occurred during 1 month after the Mid Niigata Prefecture earthquake (maximum seismic intensity, 7), Niigata Prefecture, Japan, which occurred on October 23, 2004, and to assess the risk factors for APE after the earthquake. This earthquake was marked by an unusually large number of strong aftershocks, which severely hampered rescue efforts and left evacuees extremely concerned for their safety. According to the Meteorological Agency, 25 aftershocks with a magnitude of 5 or more hit the region. Therefore, thousands of people were forced to camp out in public facilities, tents, or even in their vehicles for a prolonged period.

MATERIALS AND METHODS

In November 2004, we sent questionnaires to hospitals, except psychiatric hospitals, listed in the Japanese Hospitals Directory, 2003 to 2004, in Niigata Prefecture.[11] The same survey was also sent to hospitals outside the prefecture, where emergency cases were transferred during that period. We sent the same questionnaires repeatedly (a total of five times) to hospitals if there was no reply.

The registry consisted of out-of-hospital cases of newly diagnosed APE between October 24, 2004, and November 23, 2004. In addition to general risk factors for APE, including immobilization, obesity, recent surgery, recent trauma, active malignancy, cardiovascular disease, chronic respiratory failure, pregnancy and delivery, and past history of VTE, we examined whether the subjects stayed in a car or temporary public shelter.

The population and number of evacuees staying in a temporary public shelter 1 week immediately after the earthquake was based on data provided by the Niigata Prefectural Office.[12] The mean ratio of evacuees to the population during the first week after the earthquake was calculated from these data. Cities, towns, and villages in the Niigata Prefecture were classified into two categories (high evacuee rate area and low evacuee rate area) using these ratios. A ratio of > 5% comprised the high evacuee rate area, and a ratio < 5% comprised the low evacuee rate area.

Statistical Analysis

Statistical analysis was performed using SPSS 13.0 (SPSS, Inc., Chicago, IL). Continuous variables were analyzed by Mann-Whitney test and expressed as mean (± standard deviation). Nonordinal categorical data were analyzed by Fisher's exact test or binomial distribution. Relative risks were analyzed by Poisson regression analysis.

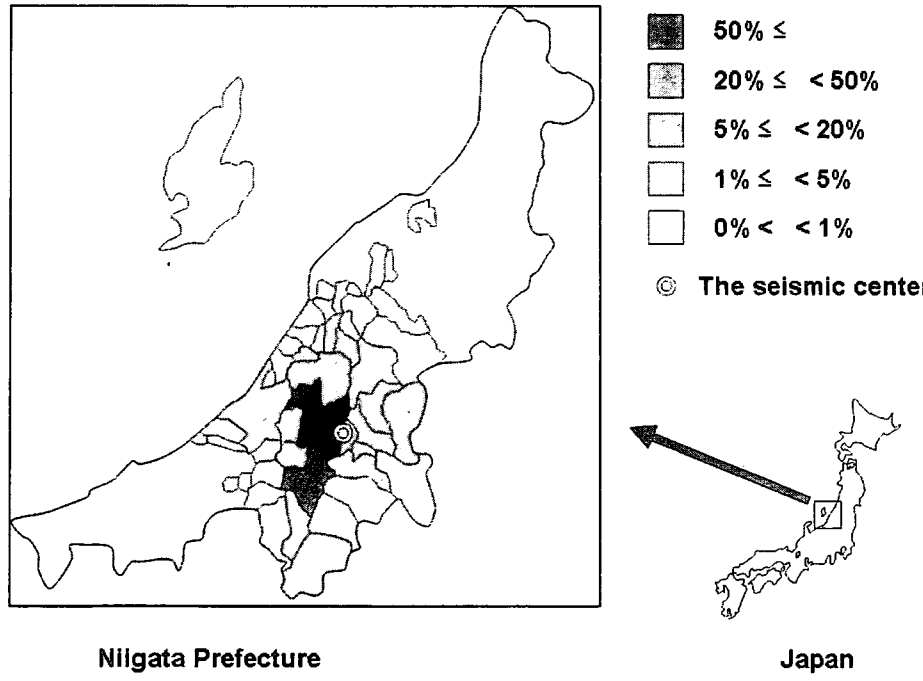

Figure 1 Mean ratio of evacuees to population in the first week immediately after the Mid Niigata Prefecture earthquake, Niigata Prefecture, Japan.

RESULTS

A total of 122 letters were sent to the departments and hospitals and 117 replies were received (response rate, 95.9%). As shown in Fig. 1, the mean ratio of evacuees to the overall population was higher near the seismic center.

Out-of-Hospital Cases of APE

There were 10 cases with APE out of hospitals (one male and nine females; age 66.1 ± 14.9 years old; Table 1 and Fig. 2). Diagnostic imaging techniques were not used in two patients who died. These two patients complained of dyspnea just after getting out of a car, and then experienced cardiopulmonary arrest. Their death certificates indicated pulmonary embolism as the cause of death. Diagnostic imaging techniques were performed in all other eight cases (contrast-enhanced computed tomography in seven cases, perfusion lung scan in two cases, and pulmonary angiography in one case). The age of the living patients was 61.6 ± 15.7 years (range, 43 to 79 years) in the high evacuee rate area, and 76.7 ± 5.5 years (range, 71 to 82 years) in the low evacuee rate area ($p = 0.18$). The male-to-female ratio was 0:7 in the high evacuee rate area ($p = 0.008$) and 1:2 in the low evacuee rate area ($p = 0.38$; Fig. 3). The relative risk of APE was higher in the high evacuee rate area and among women (Table 2). All patients from the high evacuee rate area had stayed in their cars but none had done so in the low evacuee rate area. The period of staying in a car ranged from 1 to 5 days (Fig. 4). One of seven in the high evacuee rate area and all cases in the low evacuee rate area had general risks for VTE (Table 3).

Table 1 Number of Patients with Acute Pulmonary Embolism (APE) and Population in Each Area

	Number of APEs		Population	
Area	Women	Men	Women	Men
High evacuee rate area	7	0	190,562	182,107
Low evacuee rate area	2	1	1,071,159	1,004,197
Total	9	1	1,261,721	1,186,304

High evacuee rate area, evacuees to population ≥ 5%; low evacuee rate area, evacuees to population < 5%.

DISCUSSION

APE is encountered more often in persons who remain seated for a long period of time. Most of these patients do not have known pre-existing risk factors for VTE. We divided the Niigata Prefecture into two areas (high evacuee rate area and low evacuee rate area) according to the number of evacuees compared with the overall population. APE occurred in seven of 372,669 people (0.19%) in the high evacuee rate area, whereas the overall incidence of out-of-hospital patients with APE in Japan has been reported as 0.01% per month.[13,14] Our data suggest that sleeping in an emergency shelter per se was not a significant risk factor for APE, but that sleeping in an automobile appeared to be a risk factor. The period of staying in a car ranged from 1 to 5 nights. The long-flight syndrome is known to occur in flights longer than 3 hours.[15] In addition to sitting during long periods, low humidity, hypoxia, and insufficient fluid intake have been described as cabin-related risk factors.[16] Therefore,

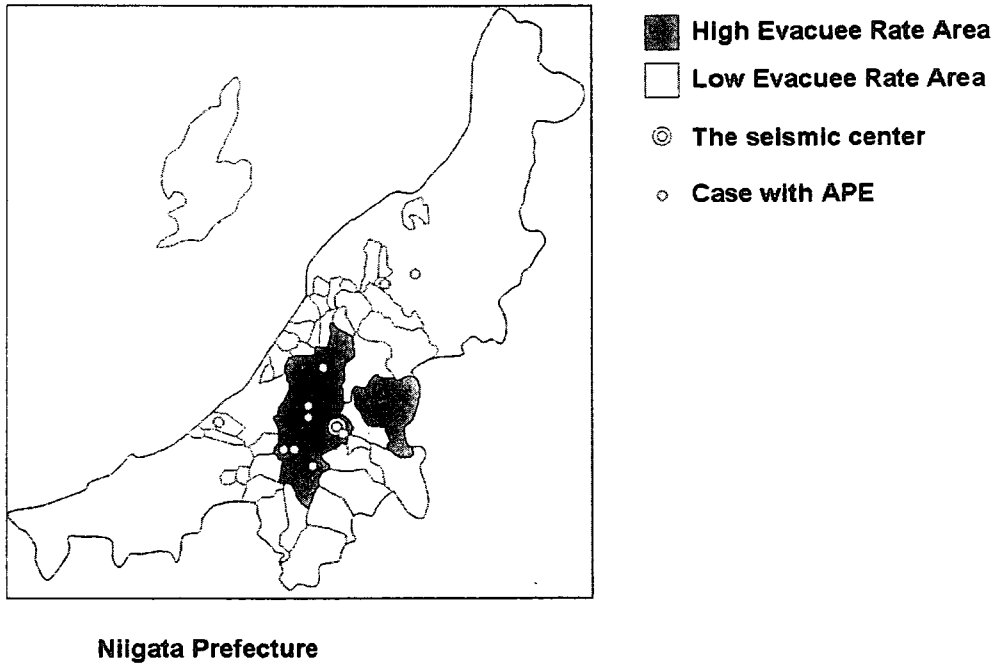

Figure 2 Geographic distribution of out-of-hospital cases of acute pulmonary embolism (APE). High evacuee rate area, area with a ratio of evacuees to population ≥ 5%; low evacuee rate area, area with a ratio of evacuees to population < 5%.

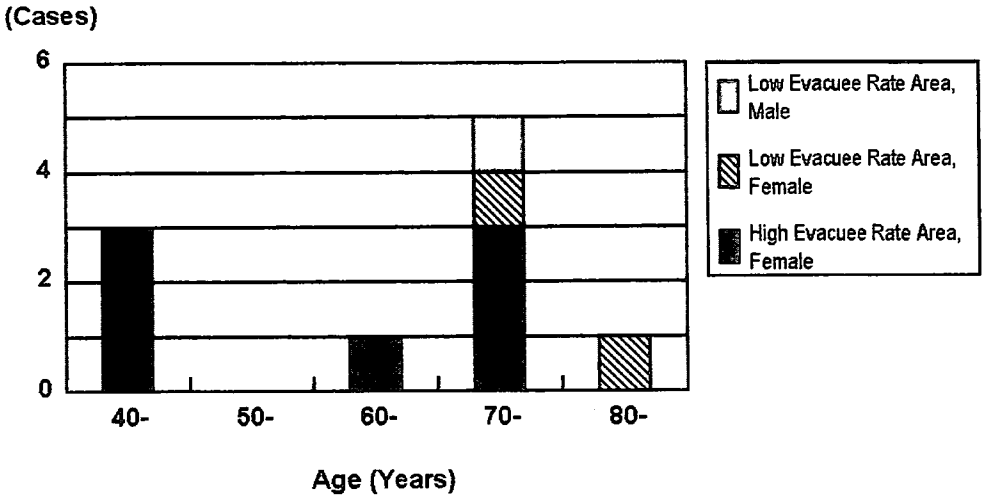

Figure 3 Distribution of acute pulmonary embolism cases by age, gender, and area. High evacuee rate area, area with a rate of evacuees to population ≥ 5%; low evacuee rate area, area with a ratio of evacuees to population < 5%.

although the results of studies regarding the long-flight syndrome cannot be extrapolated directly to sitting in a car, it appears possible that APE occurred when sitting in a car even for only 1 night, especially given that thrombosis after long car trips also has been reported.[2]

There apparently are more female than male patients with APE in Japan.[13,14,17–19] However, when the population composition is taken into consideration, deaths from APE in Japan are more frequent in men than in women,[20] as in Western countries.[21,22] Age is a risk factor for APE,[23] and there are many more older women than men in Japan. This should result in more female cases of APE in Japan. Our study indicated that women were at greater risk and the present results resemble those of the long-flight syndrome. Lapostolle et al[7] reported that 75% of the patients with APE associated with air travel were women, and Morio[24] reported 87% of the patients with APE associated with air travel were women. The compression of veins in the popliteal area on the edge of a seat could be a contributing factor to venous stasis and deep vein thrombosis after a long period of sitting in a chair,[25] especially in short persons.[24] The same mechanism may contribute to the development of APE when sitting in a car.

Table 2 Relative Risk for Acute Pulmonary Embolism

	Relative Risk	95% CI	*p*
Area			
Low evacuee rate area	1.00		
High evacuee rate area	13.09	3.38–50.60	0.0002
Gender			
Male	1.00		
Female	8.55	1.08–67.49	0.04

CI, confidence interval; high evacuee rate area, evacuees to population ≥ 5%; low evacuee rate area, evacuees to population < 5%.

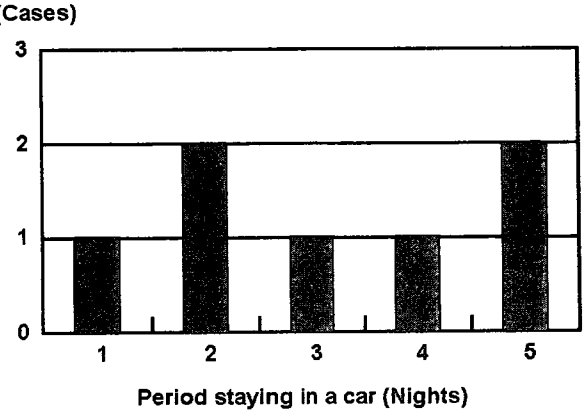

Figure 4 Number of nights in an automobile in patients with acute pulmonary embolism.

At the same time, earthquake-induced stress seems to induce changes in hemostatic factors, as demonstrated by increased levels of D-dimer, von Willebrand factor, and tissue-type plasminogen activator antigen.[26] During the Hanshin-Awaji earthquake, the increase in cardiovascular disease was significantly greater in women

Table 3 Mortality and Risk of Acute Pulmonary Embolism

Parameter	High Evacuee Rate Area (n = 7)	Low Evacuee Rate Area (n = 3)	*p*
Mortality	42.9%	33.3%	1.00
Sleeping in automobile	100.0%	0.0%	0.008
Sleeping in emergency shelter	14.3%	0.0%	1.00
General risk	14.3%	100.0%	0.03

High evacuee rate area, evacuees to population ≥ 5%; low evacuee rate area, evacuees to population < 5%.

than in men, and the mean posttraumatic stress disorder reaction index score was also significantly higher in women.[10] These findings suggest that emotional stress could have a greater effect on women. Therefore, the high number of women with APE in our study suggests that mental and physical stress related to an earthquake might trigger VTE.

There was no significant difference between the ages of APE cases in the high evacuee rate area and in the low evacuee rate area. It should be noted, however, that peaks in the cases of APE in the high evacuee rate area were seen not only in the elderly but also in those in their 40s. These numbers were small, but may reflect a difference in the age distribution of APE reported to date. APE is a multicausal disease,[23] and is believed to occur when new risk factors appear in addition to pre-existing ones. Given that only one case had a known general risk for APE in the high evacuee rate area in this study, it would appear that staying in a car alone is a risk for APE.

In conclusion, APE after the Mid Niigata Prefecture earthquake was more frequent in persons who spent long periods of time in cars, and was more frequent in females than males.

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ITP（特発性血小板減少性紫斑病）と *Helicobacter pylori* 除菌療法について

藤村　欣吾

要　旨

特発性血小板減少性紫斑病（ITP）は後天性の血小板減少症で，出血症状を主徴とし，発症に血小板膜に対する抗体が関与する自己免疫疾患の一つと考えられ副腎皮質ステロイド療法や摘脾療法が治療の基本である．最近本疾患の中でヘリコバクタピロリ菌（HP菌）陽性症例に対して除菌療法により約40～60％の症例が血小板増加効果を示し，HP菌が一部のITP症例の発症に関係していることが示唆され注目を浴びている．HP陽性ITPの臨床的特徴は①HP感染頻度の高い中高年者のITPが多い．②ITPとしての重症例は少ない．③骨髄巨核球数は正常よりも増加している症例が多い．④除菌成功群は不成功群に比し有意に，長期の血小板増加反応が認められる．⑤除菌前の血小板数，ITPとしての前治療は血小板増加反応に影響しない．⑥除菌療法による血小板増加反応はITPとしての罹病期間が短い症例に有意に多い．⑦血小板増加反応は除菌後1カ月で認められる．⑧除菌療法の有用性の報告は日本，イタリア，台湾など一部の国に限られている．⑨HP陽性ITPにはHLA-DR，DQ領域に特徴がある，などである．HP陽性ITPに対して除菌療法がITP治療として有用であり，HP関連ITPとしてITPの中に位置づける事が可能と考えられる．HP菌感染とITPの発症にはCag A抗原と血小板膜抗原との間の所謂分子相同性機序が有力である．

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Key words：ITP, *Helicobacter pylori*, eradication, molecular mimicry

はじめに

特発性血小板減少性紫斑病（ITP，idiopathic thrombocytopenic purpura）は主として皮膚や粘膜の紫斑を主体とする出血症状を示す後天性の血小板減少症である．慢性に経過する所謂慢性型は成人に多く特に女性が男性の2.5倍多い．本邦における最近の調査では年齢分布は男女とも20歳頃から増加し始め，51歳～70歳にピークを認めている．

年間発生率は人口10万人当たり1.25人で発症機序の解明，診断・治療法の確立を目指して厚生労働省の難病指定を受けている疾患である．

従来より血小板膜に対する自己抗体が産生され血小板が破壊されることに因る血小板減少機序が想定され，さらに最近抗原認識機構が明らかになるに伴い自己免疫疾患として鮮明にされつつある．すなわち血小板膜糖タンパク抗原，GPIIb/IIIa，GPIb/IX，GPVI，GPV等に対する自己抗体やこれらに対する抗体を産生するB細胞も同定，定量化することが可能となってきた[1]．

自己免疫機序が発症に関係していることからITPの治療は副腎皮質ステロイドを中心とした免疫抑制療法や血小板破壊場所，並びに抗体産生の中心的役割を果たす脾臓の除去（摘脾療法）が定着している．それら一連による治療成績は大

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まかには約40%の完全寛解，所謂治癒といって良い症例と，日常生活には何ら支障がないが軽度の血小板数減少が持続する部分寛解と考えられる症例が40%，血小板減少に対する何らかの治療介入が必要な症例が約20%である．このうち治療介入症例，主として難治症例に対する新たな治療戦略が求められる一方では，部分寛解症例についても治癒が望まれている．このような中にあって従来とは全く異なる治療法が一部のITP症例に効果のあることが報告された．

1998年Gasbarriniらによって初めてヘリコバクターピロリ菌陽性（HP陽性）のITP症例において除菌療法後に血小板数が増加した症例が報告された[2]．以来ヘリコバクタピロリ菌（HP菌）除菌療法は一部のHP陽性ITP症例においては血小板増加反応を手軽に期待させる治療法として脚光を浴びている．

ここではHP菌陽性ITP症例に対する除菌療法の本邦並びに世界的現状を述べ，HP菌とITPの関連について考えるとともに除菌療法の位置づけについても紹介する．

1. ヘリコバクターピロリ菌感染と全身性疾患

HP菌は1983年に発見されたグラム陰性桿菌で上部消化管疾患の発症機序や治療概念に大きな変化をもたらした．すなわち胃粘膜局所に持続感染し，好中球を始めとした炎症性細胞浸潤を来たし萎縮性胃炎，胃潰瘍の主たる原因として考えられ，さらには胃がんや胃のリンパ腫（MALTリンパ腫）の発症との関連が示されている．1994年には疫学的研究からType I（definite）のがん源因子として認定されている[3]．

胃粘膜局所感染であることから上部消化管疾患との関連は容易に理解可能であるが，最近では全身性疾患との関連が注目を集めている．例えば甲状腺炎やシェグレン症候群，関節リウマチ，膜性腎症など自己免疫疾患との関連を始めとして血液疾患では悪性貧血，自己免疫性好中球減少症，シェーンライン・ヘノッホ紫斑病，やHP除菌により経口鉄剤治療抵抗性の鉄欠乏性貧血の改善，MGUSの一部に単クローン性ガンマーグロブリン血症が改善する例が報告され，さらには一般の動脈硬化症や冠動脈疾患との関連も示唆されている[4]．このように多くの全身性疾患との関連性が報告されているが，中には疑問視されている疾患もありどのような機序で全身性疾患が生じるのか明らかではない．この中にあってITPとHP感染については最近になって臨床的論文が最も多くなり，除菌治療効果から両者の関連性を強く示唆する報告が多い[2,5~11]．

2. ITPにおけるヘリコバクターピロリ菌感染頻度

HP菌感染症は広く全世界に認められるが，国，地域，人種，年齢によって感染率が異なる特徴がある．感染様式は経口感染で，感染源として，吐物，唾液，便，に加え水が伝播経路として重視されている．胃酸分泌能や免疫能が十分に発達していない乳幼児期に感染し以後慢性に経過するといわれ，幼児期の衛生状態，社会経済的状況がHP感染率を規定する[3]．

一般人口の感染率は加齢に伴って上昇し，発展途上国では中高年の80%以上であるのに対し，先進国，工業国では40%前後に留まっている．

慢性ITPにおけるHP感染率も一般人口と同様に加齢と共に上昇し，イタリア，日本からの報告では，一般人口の感染率と同様に中高年症例の70~90%と先進国でも頻度が高く，年齢をマッチさせた一般人口との間では感染率に差はない．従ってITPに感染率が高い訳ではなく，HP感染者の一部にITPが発症したものと考えられる．

小児慢性ITPにおいては北欧（フィンランド）ではHP菌陽性例は認められないが，台湾，日本においては陽性率40~20%との報告があり小児のHP感染率は成人に比し低いがその感染率は社

表1. 成人慢性ITP症例におけるピロリ菌陽性率と除菌による血小板増加効果（2006年5月）

報告者	報告年	症例数	ピロリ菌感染率 (%)	除菌成功症例数	血小板増加反応例 (%)	平均観察期間 (月)
Gasbarrini et al (伊)[2]	1998	18	11 (61)	8	8 (100)	4
Emilina et al (伊)[5]	2001	30	13 (43)	12	6 (50)	8.3
Jarque et al (西班牙)[7]	2001	56	40 (71)	23	3 (13)	24
Kohda et al (日)[6]	2002	48	27 (56)	19	12 (63)	14.8
Hino et al (日)[21]	2003	30	21 (70)	18	10 (56)	15
Hashino et al (日)[22]	2003	22	14 (64)	13	5 (39)	15
Ando K et al (日)[23]	2003	61	50 (82)	27	16 (59)	11
Michel et al (米)[9]	2004	76	16 (21)	14	0	11.5
Takahashi et al (日)[10]	2004	20	15 (75)	13	7 (53.8)	4
Fujimura et al (日)[11]	2004	435	300 (69)	155	88 (57)	12＜
Ando T et al (日)[24]	2004	20	17 (85)	17	15 (85)	24
Sato et al (日)[25]	2004	53	39 (74)	27	15 (55.6)	6
Inaba et al (日)[26]	2005	35	25 (71)	25	11 (44)	6
Veneri D et al (伊)[27]	2005	43	43	41	20 (49)	31.2
Stasi R et al (英, 伊)[13]	2005	137	64 (47)	52	17 (33)	12＜
Suzuki et al (日)[12]	2005	36	25 (69)	23	10 (44)	6
Suvajdzic N et al (英)[28]	2006	54	39 (72)	23	5 (26.1)	18
計		1,174	759 (64.7)	510	248 (48.6)	13.1＜

会背景，環境によって異なっている．

小児に多い感染を契機とする急性のITPについてはHP感染との関連は有意ではなく，急性ITPの発症にHP菌感染は関わっていないとの報告がある．

3. ピロリ菌感染ITPにおける除菌療法による血小板増加について

1998年のGasbarriniらの報告以来除菌療法による血小板増加効果を検討した報告が多くなされている．その一覧を表1に示したが除菌による血小板増加効果は国によって有効率に差があり，スペイン，英国，米国からの報告では除菌による血小板増加効果はほとんど認められないか増加反応を示す症例が少ない．スペインの報告では13%がPRとなっているに過ぎない[7~9]．一方イタリアや日本からの報告では一部を除き約40%以上に血小板の増加反応が認められている(33~100%)[5,6,10,11]．

このように除菌後の血小板増加効果について大まかに2極化した報告になっているのが現状である．この原因は不明であるが1)対象者の免疫学的背景に差がある，2)地域的に感染したピロリ菌株によって発現している抗原性の程度が異なる(Cag，Vag，がコードする蛋白抗原，Lewis（Le）抗原など）等が推測されている．

4. HP菌陽性ITP症例における胃病変とピロリ菌株

HP菌陽性ITP症例の胃病変について検討した報告では，殆どpangastritis或いは胃体部に著明な胃炎の所見を示している．また感染菌株について本邦の報告では血小板減少を伴わない単なる胃，十二指腸潰瘍症例と同様で，Cag A，Vac A，ice A，IL-8の発現なども他のHP感染消化器疾患と差は無いとされている．従って本邦内では血小板減少を引き起こす特有の菌株や菌の性状は見当たらない[12]．

表2. ヘリコバクタピロリ菌陽性ITPと陰性ITPの初診時臨床的背景(文献11より)

	HP 陽性ITP	HP 陰性ITP	
症例数	300	135	
男/女	1/2.6	1/2.65	
平均年齢*(歳)	58.92±13.76	47.36±15.87	p < 0.005 (odds 1.72)
罹病期間(年)	8.18±6.8	8.74±7.23	
出血傾向			
あり	161	85	
なし	133	46	
不明	6	4	
血小板数(万)			
5～10	61	24	
3～5	76	25	
1～3	115	53	
<1*	37	27	p = 0.066 (odds 0.4)
不明	11	6	
巨核球数			
増加*	140	51	p = 0.011 (odds 2.03)
正常	110	59	
減少	5	4	
不明	5	21	

5. 本邦のレトロスペクティブ共同研究によるHP菌陽性ITPに対する除菌療法の血小板増加反応について[11]

表1に示した除菌療法による血小板増加効果に関しては報告によって，除菌前の血小板数，ITP治療の影響，除菌後のITP治療の有無，除菌による血小板数の改善の基準，観察期間などが欠落していたり，統一性がなく除菌が血小板増加に関係していることを疑問視する報告もあった．

これらの問題点を踏まえ厚生労働省研究班において2002年7月から2003年12月の18カ月間に血液専門11施設の協力の下にレトロスペクティブ共同研究を行った．

1) ピロリ菌陽性ITPの臨床病態(表2)

慢性ITP435例のうち300例(69%)がHP陽性であった．年齢別HP陽性ITPの頻度は，20歳代は40%以下で，40歳代では約50%であるが以後加齢と共に上昇し，50歳代では70%以上が，60歳以上では80%以上がHP陽性である．これは本邦における一般人口に見られる年齢別感染率と類似している(図1)．

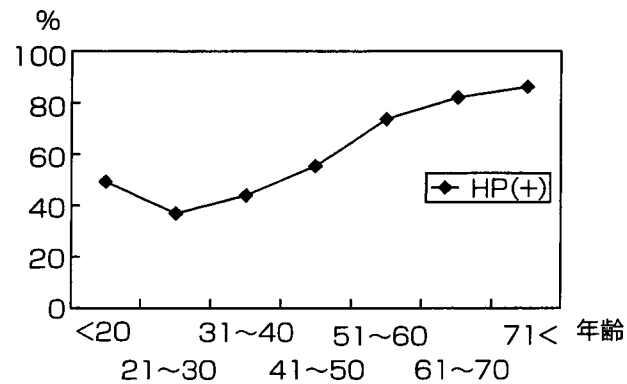

図1. ITP症例における年齢別ピロリ菌陽性頻度
(文献11より)

HP菌陽性ITP症例群とHP菌陰性ITP症例群との臨床的背景については(表2)，年齢はHP菌陽性群が陰性群に比し有意に高いが，性差，ITP罹病期間，出血症状を中心とする臨床症状，において両群間で差は認められない．しかしHP陽性ITPでは有意に初診時血小板数は激減してい

表3. 除菌後12ヶ月を経た時点での血小板増加反応（文献11より）

(Retrospective analysis in Japan 2003)

除菌直前の血小板数（×10⁴）	(%)			
	CR	PR	NR	計
除菌成功群（n = 122）				
＜1	0	2 (67)	1 (33)	3
1～3	8 (20)	23 (58)	9 (23)	40
3～5	8 (21)	16 (42)	14 (37)	38
5～10	12 (29)	10 (24)	19 (46)	41
計	28 (23)	51 (42)	43 (35)	122
除菌不成功群（n = 33）				
＜1	0	0	2 (100)	2
1～3	1 (11)	1 (11)	7 (78)	9
3～5	1 (7)	3 (21)	10 (71)	14
5～10	3 (38)	0	5 (63)	8
計	5 (15)	4 (12)	24 (73)	33

CR：血小板数＞15万，PR：血小板数3～15万，

NR：除菌前値血小板数1万以下の場合―除菌後3倍以上増加しない
除菌前値血小板数1万～3万の場合―除菌後血小板数5万以上とならない
除菌前血小板数3万～10万の場合―除菌後血小板数3万以上増加しない

る症例が少なく，骨髄巨核球数は増加している症例が多く，ITPの病態としては重症例は少ない傾向がある．HP菌感染による胃腸障害の頻度や程度は非HP感染ITPと同等で，HP菌陽性ITPは消化器症状の面から明らかにすることは出来ない．

2）除菌による血小板増加効果（表3）

HP陽性ITP300例の内228例に除菌療法が行われ，除菌効果判定が可能であった207例中161例78%に除菌が成功している．この時の除菌療法は殆どが通常のアモキシシリン，クラリスロマイシン，プロトンポンプインヒビターの3剤，7日間併用療法である．

この内除菌後12カ月以上経過観察された155例（除菌成功群122例，除菌不成功群33例）の長期予後は，除菌成功群の内79例は血小板数増加を維持し，このうち28例は除菌後無治療で血小板数15万以上となりCRの症例である(23%)．残り51例の多くは血小板数5万以上となり殆どが無治療観察（PR）となっている（42%）．43例は除菌に成功したものの血小板数の増加が認められない症例で(35%)，除菌後の血小板数は除菌前値と変わりなく軽微な増減に留まっている(表3)．すなわち除菌成功群では65%の症例が12カ月以上の間何らかの血小板増加を維持したことになる．

この頻度は除菌不成功群（9/34，27%）に比し有意に高く，ピロリ菌の除去が血小板増加に密接に関わっていることが明らかとなった．

さらにHP陽性ITPに対するピロリ菌の除去が血小板増加反応に直接的に関係していることは以下の報告からも支持される．すなわち

①SLEに伴う血小板減少においてはHP菌陽性であっても，除菌による血小板増加反応は認められず，除菌による血小板増加はITP特有のものである[6]．

②HP菌陰性ITP症例に無作為的に除菌を試みた報告では血小板増加反応を示した症例は認められず，除菌療法による非特異的血小板増加作用ではない[9]．

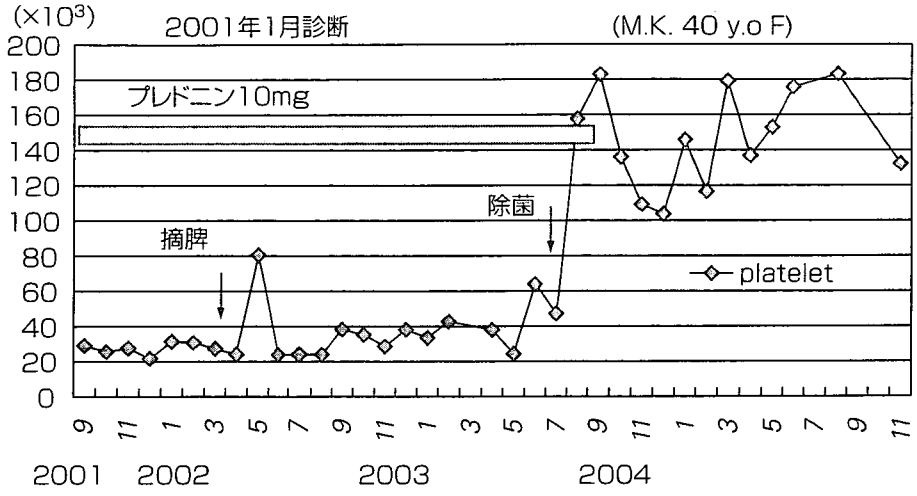

図2. プレドニン，摘脾無効　除菌有効例

③HP菌陽性ITP症例を無作為的に除菌療法を行う群（13例）と行わない群（12例）の2群に分け血小板増加反応を検討した報告では除菌群のみに血小板増加が認められる[12]，等である．今回の共同研究を含め多くの報告において除菌成功群では不成功群に比し有意に血小板増加効果が認められたことから($p<0.0001$)，この様なITP症例をHP関連ITPと呼称する根拠としている．

3）除菌による血小板増加反応の特徴

本邦での臨床研究から性差，年齢，除菌直前の血小板数，除菌直前のITP治療の有無，治療の内容など所謂ITPの臨床病態や過去の治療経過は除菌による血小板増加効果に影響しないことが判った．すなわちステロイド療法や摘脾に対して不応性の症例に対しても血小板増加が認められる点は大きな利点である(図2)[6,11]．Stasiらは除菌前の血小板減少が軽微である症例(4.8万前後）群に血小板増加効果が有意に認められ予後を予測する上で参考になると報告しているが，本邦の成績では同様の傾向はあるものの有意差は認められていない（表3)[13]．

しかし極度に血小板数が少ない1万以下の症例では血小板増加反応が認められても軽度である傾向がある．

血小板増加反応は除菌後1カ月には認められ以後徐々に増加し，再発例がなく1年以上血小板増加が持続することも特徴である．多くの報告でも血小板増加反応は長期に持続しており再発例はないか少ない．

ITPとしての罹病期間が短い群（6.52±4.67年）が長い群（9.85±7.77年）に比し有意に除菌成功後の血小板増加を来たした（$P<0.0001$)．Tasaiらも罹病期間1年前後の症例が3年未満の症例に比し血小板増加反応が良好との報告を行っている[13]．

4）除菌療法の副作用

ITPにおける除菌の副作用に関して詳細な報告はなく，本邦の集計では222例中39例(17.6%)に何らかの副作用が認められた[11]．多くは消化器症状で25例（64%）に認められ，その内訳は軟便，下痢，胃部不快感などであった．この他蕁麻疹などの皮疹9例(23%)が認められている．重篤な症例は血小板減少が増悪した1例のみで安全におこなえる治療と思われる．ただし血小板数が1万以下の症例に関しては消化管出血，その他出血傾向の増悪など慎重な判断が必要である．

6. ヘリコバクタピロリ菌感染による血小板減少機序

従来リウマチ熱，ギラン・バレー症候群，リウマチ様関節炎，I型糖尿病などいくつかの自己免疫疾患の病因に感染症が関係している事が明らかにされているが，ITPの一部もHP菌が発症に関連している事が臨床的に示唆される．

HP菌体成分のうち細胞外毒素である95Kdの空胞化因子VacA（6面体陰イオン選択性，電位依存性チャンネルを形成するとともにミトコンドリア膜を標的としアポトーシスを引き起こす）やCag-PAI（cag pathogenicity island）がコードする蛋白の一つであるCagA（cytotoxin-associated antigen A）は直接細胞障害や炎症反応，細胞増殖反応に関わるとともに高い抗原性を有しており，菌体表層のLewis抗原様側鎖と共に，これら抗原に対する免疫反応が検討されている[3]．

しかし一般のHP菌陽性症例においては，HP菌に対する特異的な全身性の免疫反応は末梢血リンパ球の検索からは認められず，また臓器非特異的，特異的自己抗体（抗核抗体，抗平滑筋抗体，抗マイクロソーム抗体など）の出現頻度はコントロールと差がないと報告されている[14]．しかし最近小児においてはHP菌陽性群においては臨床症状とは関係なく陰性群に比し，胃壁細胞抗体，マイクロゾーム抗体，の出現頻度が有意に高く，小児におけるHP菌感染は自己免疫的胃炎や他の自己免疫疾患の誘引となると報告され[15]，局所のHP感染から全身的免疫反応への伸展の可能性を示唆している．

除菌により血小板が増加したITP症例ではTh1/Th2の比が除菌後上昇する事は，HP菌感染が全身的な免疫反応の不均衡をひき起していることを裏付け興味深い．また最近HP陽性ITP症例においては末梢血において特異的なT cellのクローナルな増殖が認められ除菌効果に伴ってクローンが消失すると報告され，HP菌に対する全身的な免疫反応が血小板減少と関連している事が示されている[16]．

局所感染から血小板減少を引き起こす機序として以下のような説が提示されている．

1）Lewis抗体の関与

HP感染症例においては高いLewis抗体価を示す例がある．この抗Lewis抗体が認識するエピトープを有する組織にこの抗体が結合し自己免疫疾患を起こす（molecular mimicry）．例えば胃壁細胞のH^+-K^+-ATPaseの一部はLewis抗原エピトープを有し抗Lewis抗体が壁細胞障害を生じ胃炎を引き起こす説もある．

この抗Lewis抗体が血小板に非特異的に吸着され血小板減少を引き起こすと考えられる[17]．

2）分子相同性

従来より微生物由来の，たとえばリポポリサッカライドやDNAなどはアジュバントとして働き無関係の抗原に対して容易に免疫反応を起こす結果，自己抗原に対しても異種抗原と同じようにT-cellの反応を引き起こし易いと言われている．また一方，抗原分子相同性により（molecular mimicry）微生物由来の抗原ペプチドと自己抗原ペプチドの間に交差性があれば自己抗体として認識され自己免疫疾患が発症すると推測される．

HP菌陽性ITP血小板から誘出した抗体はHP菌のCag A抗原と反応することが免疫ブロッティング法で明らかにされた[10]．さらに除菌により血小板数が回復するとCag A抗原と反応する抗体は誘出液中には認められなくなるが，除菌による血小板数の増加が認められない症例においては抗体の消失は認められない．また興味あることにHP菌陰性ITP症例の血小板誘出液もCag Aを認識することから，HP陰性ITPの血小板に結合している自己血小板抗体はCagAと反応し抗原相同性があるものと理解される．CagAに対する抗原相同性については同様な方法で検討したフランスのグループは否定的な検討結果を報告している[8]．これには本邦と欧米との間でHP菌株に差がある可能性もありCagA抗原との分子相同性に

ついては今後多くの地域で検討すべきである．またCag A IgG抗体価が高い症例には除菌による血小板増加反応を示す症例が有意に多く，除菌効果を予測する事が可能であるとの報告は，Cag A抗原がITP発症の免疫反応に関わっている事を別の角度から示唆したものである[12]．

いずれにしてもCag A抗原とこれに反応する抗体が血小板減少の発症に関連している報告が集積されつつあるのが現状である．

3）vWF（von Willebrand factor）と抗HP菌抗体による血小板活性化反応に伴う血小板減少[18]

あるHP菌株はvWF，抗HP菌抗体の存在下で血小板凝集反応を引き起こすことが報告された．この凝集反応はHP菌がvWF，抗HP菌抗体を結合し，それぞれが血小板膜GPIb/V/IX複合体およびその近傍に位置するとされるFcγRIIAを介してシグナルがGPIIb/IIIa複合体へ伝達され血小板凝集反応が生じると考えられている．血小板活性化が局所の炎症反応，潰瘍形成に，また心血管障害に関係し，さらには血小板活性化による慢性的血小板消費による血小板減少が引き起こされるとする報告もある．

これら諸説のうち臨床研究から分子相同性を示唆する機序が理解しやすい．HP菌に対する免疫反応の発現についてはHP菌の菌体自体が免疫反応に関わる必要はなく，むしろHP菌が産生するCag A抗原のように胃粘膜細胞に進入し細胞の増殖，分化に影響を与えると共に，炎症反応を引き起こし細胞が破壊され抗原認識細胞を始めとする免疫担当細胞とCag A抗原が接触する結果，免疫反応が引き起こされる可能性がある．また感染からITP発症までに時間が経過する点については自己抗原認識のためのT細胞のプライミングに時間が必要で，さらにまた抗原エピトープの拡大，に要する時間と考えれば理解可能である．今後はこれらの仮定を証明することが必要である．

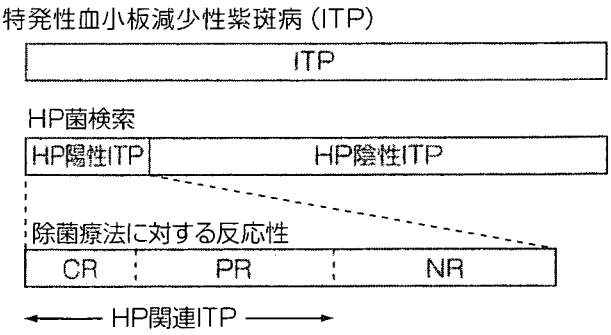

図3．HP関連ITPの位置付け（仮説）

7．ピロリ菌感染によってITPを生じる症例の特徴

ピロリ菌感染者は非常に多いにもかかわらずITPを発症する症例はそのごく一部で，多くはITPを発症しない．この事に関しては例えばCagAと交叉反応する血小板抗原を認識する免疫反応の個体差が関係していると考えられ，HLA系を検索した報告がある．それによるとHP菌陽性ITPではHLA-DRB1*11，14，とHLA-DQB1*03がHP菌陰性ITPに比し有意に高く，HLA-DRB1*03が有意に低い結果が得られている．このようなHLA系を有するヒトがHP菌感染によりHP関連ITPを発症する可能性が示唆される[19]．しかしHLA系の頻度は人種によって差があり普遍化には問題があるが，今後各々の人種間で検討し結論を出す必要がある．

8．ピロリ関連ITPに対する除菌療法の位置付け

従来よりITPは原因不明の自己免疫疾患として捉えられていた．しかしここに示したようにHP菌関連ITPが存在する可能性があり，免疫学的原因がより明確に推測されるITPの一つと捉えることができる．これらに対して従来とは全く異なった治療法で短期間に60％以上に良好な治療成績が得られたことは医療経済を含め画期的なこと

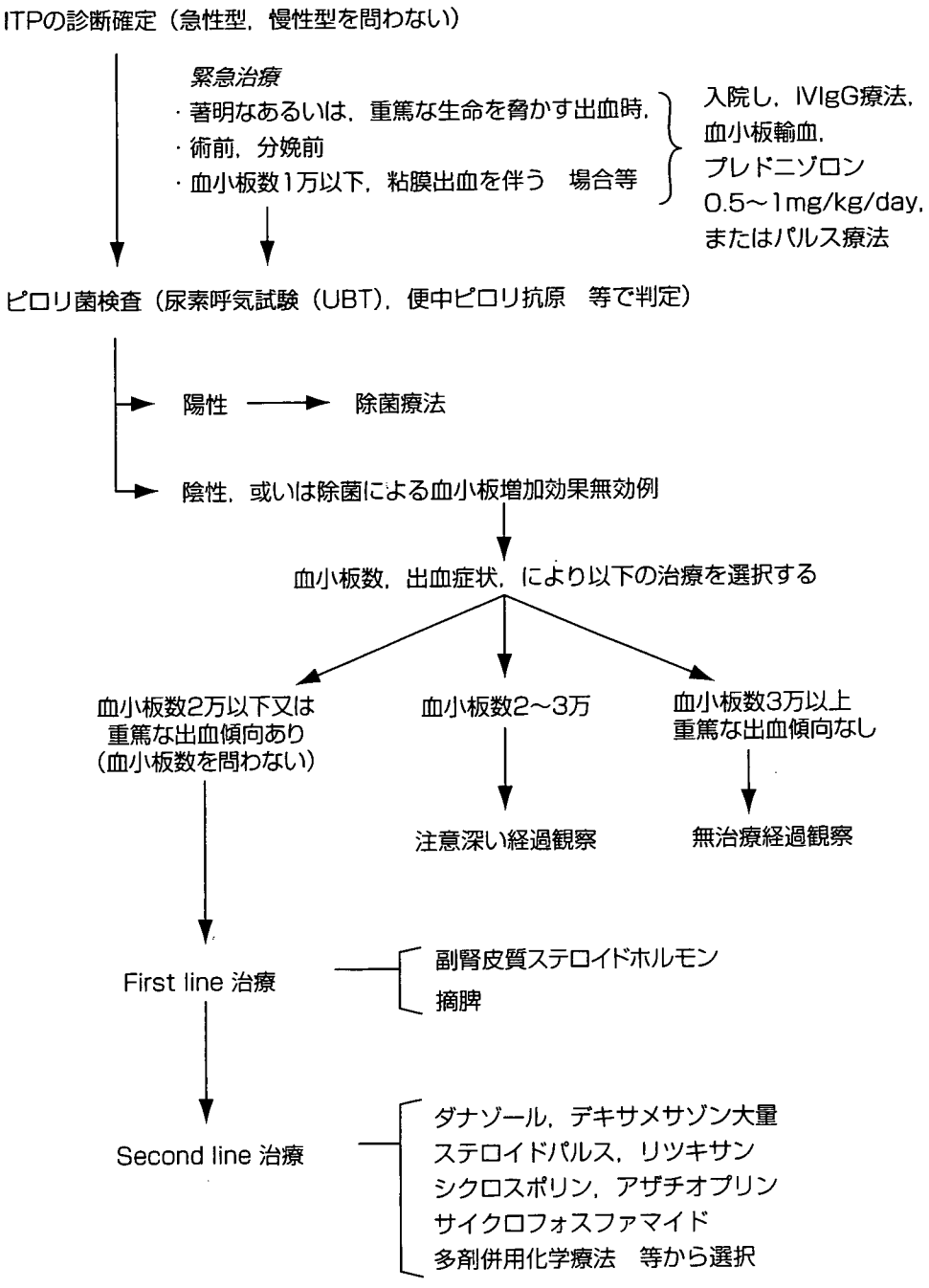

図4．成人慢性ITP治療ガイドライン（2004）（文献20より）

である．特に従来よりITPに対して第一選択薬とされているステロイド治療を回避することが出来る症例が認められることから副作用，合併症対策への治療費，治療期間が削減されより良いQOLが期待できると考えられる．

そこでHP菌陽性ITP症例においてはまずHP菌の関与を除き，除菌により血小板増加反応を示した症例はHP関連ITPとしてITPの中で位置付けることを考えている（図3）．

9．HP除菌を考慮したITP治療ガイドライン（図4）

以上を踏まえてITP治療ガイドラインを作成した．その概略として

1）ITP治療の緊急性を要する症例は別として，