Mod Rheumatol (2006) 16:92–96
DOI 10.1007/s10165-006-0456-8

CASE REPORT

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A case of idiopathic portal hypertension associated with rheumatoid arthritis

Received: June 17, 2005 / Accepted: January 6, 2006

Abstract A 53-year-old woman who had been diagnosed with rheumatoid arthritis was found to have thrombocytopenia, splenomegaly, and gastric varices. She was diagnosed as having idiopathic portal hypertension on the basis of liver biopsy and angiography. Treatment with prednisolone was not sufficiently effective for thrombocytopenia. After transabdominal devascularization with splenectomy, thrombocytopenia subsided and gastric varices disappeared. In this case, the autoimmune mechanism as well as hypersplenism was suspected of being involved in the mechanism of thrombocytopenia.

Key words Idiopathic portal hypertension (IPH) · Rheumatoid arthritis (RA) · Splenectomy · Steroid therapy · Thrombocytopenia

Introduction

Idiopathic portal hypertension (IPH) is characterized by portal hypertension, splenomegaly, and anemia, in the absence of liver cirrhosis or occlusion of the hepatic or extrahepatic portal veins,[1] although the etiology remains unknown. Recently several reports have described the association between IPH and autoimmune diseases in Japan, and the autoimmune mechanism is considered to be one of the aspects of pathogenesis of IPH.[2–6] In this report we describe a patient with IPH associated with rheumatoid arthritis (RA) whose platelet count showed interesting changes due to steroid therapy and splenectomy.

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Case report

A 49-year-old woman was diagnosed with RA by an orthopedic surgeon in Fukushima Rosai Hospital in 1997 and was treated with 150 mg/day of D-penicillamine. She underwent right total knee replacement because of deformity caused by RA in 2000 and left total knee replacement in 2002. From January 2001, progressive thrombocytopenia and liver dysfunction were observed, and in March 2001 she was admitted to the Department of Internal Medicine. She had no history of alcohol abuse. Physical examination revealed splenomegaly. An abdominal ultrasonographic study confirmed the presence of splenomegaly without evidence of liver cirrhosis or portal vein thrombosis. Laboratory data were as follows**.** Complete blood count: white blood cell count 5500/mm^3 (neutrophils 61%, lymphocytes 28%, monocytes 9%), red blood cell count 435×10^4/mm^3, hemoglobin 12.9 g/dl, hematocrit 38.4%, platelet count 4.0×10^4/mm^3 (normal, $14.0–34.0 \times 10^4$/mm^3). Serum biochemistry: aspartate aminotransferase (AST) 69 IU/l (normal, 8–27 IU/l), alanine aminotransferase (ALT) 51 IU/l (normal, 3–36 IU/l), lactate dehydrogenase (LDH) 158 IU/l (normal, 114–213 IU/l), alkaline phosphatase (ALP) 977 IU/l (normal, 90–282 IU/l), γ-glutamyl transpeptidase (γ-GTP) 190 IU/l (normal, 8–23 IU/l), C-reactive protein (CRP) 0.29 mg/dl (normal, <0.3 mg/dl), γ-globulin 2.34 g/dl, rheumatoid factor (RF) 237 IU/ml (normal, <15 IU/ml), antinuclear antibody (ANA) titer 1:160. Both hepatitis B surface antigen and anti-hepatitis C antibody were negative. Bone marrow aspiration specimens showed normocellular marrow. As she was suspected of having drug-induced thrombocytopenia and liver dysfunction, D-penicillamine was discontinued; however, her platelet count did not increase. Finally, she was diagnosed as having thrombocytopenia associated with rheumatoid arthritis, and treated with 30 mg/day of prednisolone (PSL), the platelet count increased to 15.0×10^4/mm^3 (Fig. 1). As the dose of steroid was decreased, however, the platelet count decreased, and eventually remained at $6.0–9.0 \times 10^4$/mm^3. In May 2003, she underwent esophagogastroduodenoscopy (EGDS), which

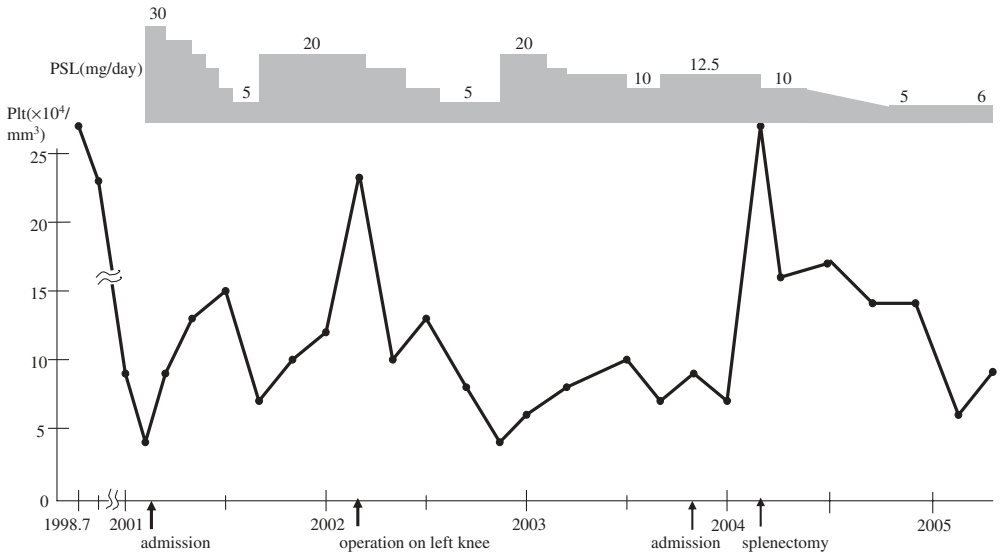

Fig. 1. Clinical course of platelet (*Plt*) count. *PSL*, prednisolone

revealed gastric varices. In November 2003, she was admitted to the Department of Gastroenterology for further evaluation.

Physical examination on admission showed splenomegaly and the operative scars on both knees, but no deformity of the hands or sclerosis of the skin. Laboratory data were as follows. Complete blood count: white blood cell count 5300/mm^3 (neutrophils 53.9%, lymphocytes 34.9%, monocytes 9.3%, eosinophils 1.5%, basophils 0.5%), red blood cell count 471×10^4/mm^3, hemoglobin 14.7 g/dl, hematocrit 44.6%, platelet count 9.0×10^4/mm^3, erythrocyte sedimentation rate 22 mm (60 min). Coagulability: prothrombin time 121.2%, activated partial thromboplastin time 33 s. Serum biochemistry: AST 45 IU/l, ALT 30 IU/l, LDH 206 IU/l, ALP 500 IU/l, γ-GTP 112 IU/l, cholinesterase 325 IU/l (normal, 200–500 IU/l), total bilirubin 2.37 mg/dl (normal, 0.2–1.3 mg/dl), direct bilirubin 0.61 mg/dl (normal, 0–0.3 mg/dl), hyaluronic acid 269.8 ng/ml (normal, <50 ng/ml), indocyanine green test at 15 min 35.4% (normal, <10%). Serology: CRP 0.1 mg/dl, γ-globulin 1.53 g/dl, IgG 1695 mg/dl (normal, 893–1838 mg/dl), IgA 300 mg/dl (normal, 102–396 mg/dl), IgM 181 mg/dl (normal, 52–253 mg/dl), RF 213 IU/ml, ANA titer 1:160 (homogeneous, nucleolar pattern). Anti-platelet antibody was weakly positive; anti-double stranded DNA antibody, anti-cardiolipin β_2-GP1 antibody, cardiolipin IgG antibody, lupus anticoagulant, antimitochondrial M_2 antibody, myeloperoxidase–antineutrophil cytoplasmic antibody, and proteinase 3-antineutrophil cytoplasmic antibody were all negative.

X-ray films of the hands revealed some bone erosions on both first and second metacarpophalangeal (MCP) joints, right third MCP joint, and right second proximal interphalangeal (PIP) joint, and narrow joint spaces on both carpal joints. According to Steinbrocker's classification of RA, the hands were in stage II.

Bone marrow aspiration specimens showed normocellular marrow and an increased megakaryocyte count.

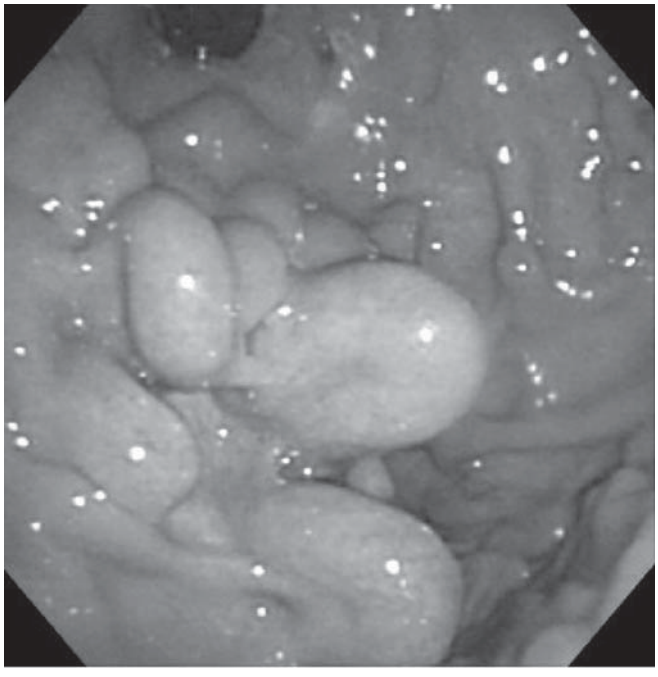

Fig. 2. Esophagogastroduodenoscopy showed gastric varices [Lg-cf, F3, RC(–)]

Esophagogastroduodenoscopy showed gastric varices [Lg-cf, F3, RC(–)] and no esophageal varices (Fig. 2). Abdominal computed tomography (CT) revealed splenomegaly and collateral veins around the fornix of the stomach. There was no evidence of cirrhosis or space occupied lesion in the liver (Fig. 3). Angiography revealed a gastrorenal shunt and no finding of obstruction in the extrahepatic portal vein. Hepatic venography showed no occlusion, narrowing, or anastomosis in the hepatic veins.

Liver biopsy specimens showed dilated aberrant veins near the portal area, and reactive mild hepatitis associated

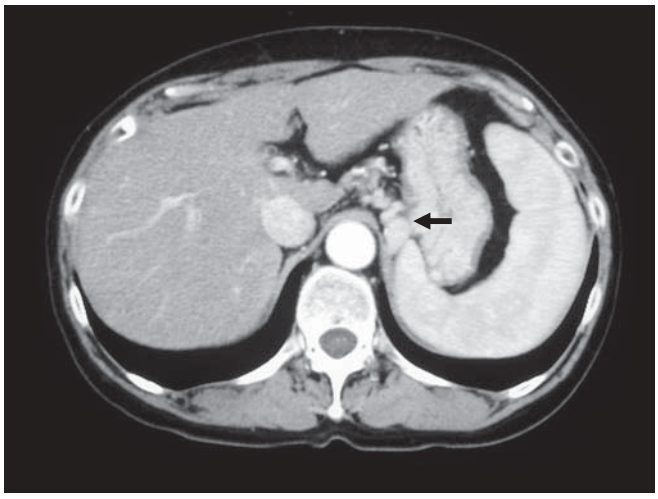

Fig. 3. Abdominal enhanced computed tomography revealed splenomegaly and collateral veins around stomach fornix (*arrrow*)

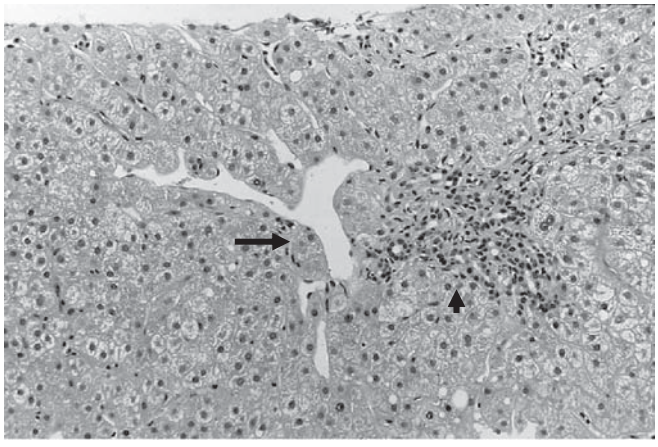

Fig. 4. Liver biopsy specimen showed dilated aberrant veins (*arrrow*) near portal area, and nonspecific reactive mild hepatitis associated with inflammatory cell infiltration (*arrowhead*) of portal area (H&E stain, ×100)

with inflammatory cell infiltration of the portal area. There was no evidence of cirrhotic change, fibrosis, infiltration of inflammatory cells of Glisson's sheath, collapse of the peripheral portal vein branches, or nodular regenerative hyperplasia (Fig. 4). Reactive mild hepatitis, which is a nonspecific finding in collagen vascular disease, was not considered to represent disease in this case. On the basis of the above findings, the patient was diagnosed as having IPH according to the guidelines.[1]

Generally, balloon-occluded retrograde transvenous obliteration (B-RTO) or endoscopic injection sclerotherapy (EIS) is chosen for the treatment of gastric varices associated with IPH. In this case, however, supposed hypersplenism was one of the causes of thrombocytopenia. To treat gastric varices and thrombocytopenia, transabdominal devascularization with splenectomy (Hassab's operation) was performed on 13 February, 2004. The presplenectomy portal vein pressure was 26.5 cmH_2O (normal, <15 cmH_2O). After operation thrombocytopenia subsided and the platelet count increased to $12.0 \times 10^4/mm^3$ (Fig. 1), and EGDS confirmed the disappearance of the gastric varices.

Discussion

Idiopathic portal hypertension is characterized by portal hypertension, splenomegaly, and anemia, in the absence of liver cirrhosis or occlusion of the hepatic or extrahepatic portal veins. In this case, IPH was diagnosed because there were splenomegaly, gastric varices, thrombocytopenia, and dilated aberrant veins near the portal area in liver biopsy specimens, and because there was no occlusion in the hepatic veins or extrahepatic portal vein.

Recently several reports have described the association of IPH and autoimmune diseases in Japan. During the last 20 years in Japan, 11 cases of IPH have been reported to be associated with systemic lupus erythematosus (SLE),[3,4,7–15] 7 with mixed connective tissue disease,[2,5,16–20] 2 with Sjögren syndrome,[21,22] 4 with systemic sclerosis,[23–25] and 5 with RA.[8,26–29] The cases of IPH associated with RA have been reported only from Japan. We suppose that the concept of IPH was created in Japan, considering that the same disease is termed noncirrhotic portal fibrosis in India[30] and hepatoportal sclerosis in the United States.[31] The majority of patients are young men in India (M:F ratio of 2–4:1, average age of 30–35 years); by contrast, the majority in Japan are middle-aged women (M:F ratio of 1:3, average age of 49.7 years).[32] It is not clear why there are such regional differences.

In patients with IPH, cytopenia due to hypersplenism is commonly seen. Fukasawa and Futagawa[33] report that 45.2% and 19.2% of patients with IPH showed leukocytopenia (<3000/mm^3) and thrombocytopenia (<5×10^4/mm^3), respectively, and that cytopenia was resolved by splenectomy. As for the mechanism of thrombocytopenia in this case, not only hypersplenism but also the autoimmune mechanism was suspected to contribute to thrombocytopenia, because (1) the platelet count increased or decreased with the dose of steroid before splenectomy, (2) thrombocytopenia progressed after splenectomy (Fig. 1), and (3) antiplatelet antibody was positive although weakly.

We considered measurement of antiplatelet antibodies after the start of steroid therapy, revealing a decreased level. We did not diagnose this case as idiopathic thrombocytopenic purpura (ITP), because thrombocytopenia associated with RA should be excluded from the diagnosis of ITP according to the criteria of ITP.[34]

Differential diagnosis of IPH and Felty's syndrome was also considered to be required in this case because of splenomegaly associated with RA. Felty's syndrome consists of leukopenia and splenomegaly associated with RA, and is characterized by vasculitis and increased susceptibility to common infections.[35] However, our patient had no history of frequent infections, leukopenia, neutropenia, or vasculitis, and so Felty's syndrome was ruled out.

Table 1. Reported cases of idiopathic portal hypertension (IPH) associated with rheumatoid arthritis (RA) in Japan

Case	Age (years)/ sex	Onset of RA to diagnosis of IPH (years)	WBC (/mm^3)	Hb (g/dl)	Plt (×10^4/mm^3)	ANA	Outcome/cause of death	Association	First author[Ref.]
1	68/F	24	7420	12.6	9.4	+	Dead/hemorrhage		Kakei[29]
2	62/F	8	2500	9.1	15.1	+	Dead/hemorrhagic shock	Chronic hepatitis B	Hashimoto[28]
3	60/M	12	3300	8.8	19.0	+	Alive		Handa[27]
4	51/F	10	2800	11.4	5.4	+	Alive	Felty's syndrome	Yoshimoto[26]
5	48/F	23	5230	9.3	3.2	+	Dead/hepatic coma after hemorrhage	SLE, pulmonary hypertension	Yasuda[8]
Present case	53/F	8	5300	14.7	9.0	+	Alive		

WBC, white blood cells; Hb, hemoglobin; Plt, platelets; ANA, antinuclear antibody; SLE, systemic lupus erythematosus

The six cases of IPH associated with RA, including the present case, are shown in Table 1. In one of them IPH was associated with Felty's syndrome,[26] and in another with SLE and pulmonary hypertension.[8] In these cases the period between onset of RA and diagnosis of IPH ranged from 8 to 24 years. Interestingly, ANA was positive in all six cases. Esophageal or gastric varices were detected by EGDS in all cases, and the cause of death was hemorrhage from ruptured varices in all three patients who died.

The pathogenesis of IPH is still unclear, but hypergammaglobulinemia and the presence of serum autoantibody are reported in patients with IPH, and the autoimmune mechanism is considered to be involved in the pathogenesis of IPH. Ohta et al.[36] report that 6.8% of the cases of IPH are associated with autoimmune diseases, and the positive incidence of ANA is 13.5%. Saito et al.[6] report that 11.9% of the cases of IPH are associated with autoimmune diseases, 26.3% have hypergammaglobulinemia, and the positive incidence of ANA is 21.9%.

We consider that steroid therapy is effective for thrombocytopenia associated with IPH as in this case. Yamamoto et al.[7] report a case of IPH associated with SLE in which steroid therapy was effective for pancytopenia, liver dysfunction, splenomegaly, and esophageal varices. To our knowledge, this is the second case of IPH in which steroid therapy was effective. Further studies are required to understand the mechanisms of IPH associated with autoimmune diseases.

References

1. Sugimachi K. The diagnosis and therapy of portal venopathy (2001) (in Japanese). In: Sugimachi K, editor. Report of the Research Committee on Portal Venopathy of Ministry of Health, Labor and Welfare 2000. Tokyo: Japan Ministry of Health, Labor and Welfare; 2001. p. 53–60.
2. Rai T, Ohira H, Fukaya E, Abe K, Yokokawa J, Takiguchi J, et al. A case of merged idiopathic portal hypertension in course of mixed connective tissue disease. Hepatol Res 2004;30:51–5.
3. Inagaki H, Nonami T, Kawagoe T, Miwa T, Hosono J, Kurokawa T, et al. Idiopathic portal hypertension associated with systemic lupus erythematosus. J Gastroenterol 2000;35:235–9.
4. Nakajima H, Motojima S, Numao T, Fukuda T. A case of idiopathic portal hypertension associated with systemic lupus erythematosus. Jpn J Rheumatol 1999;9:87–93.
5. Hirosaki S, Koide N, Ogawa H, Wada T, Sato A, Ujike K, et al. Mixed connective tissue disease associated with idiopathic portal hypertension and chronic thyroiditis. J Gastroenterol 1997;32:808–11.
6. Saito K, Nakanuma Y, Takegoshi K, Ohta G, Obata Y, Okuda K, et al. Non-specific abnormalities and association of autoimmune diseases in idiopathic portal hypertension. Hepato-Gastroenterology 1993;40:163–6.
7. Yamamoto M, Taniguchi H, Ohara M, Suzuki C, Naishiro Y, Ozeki I, et al. Beneficial effect of glucocorticosteroids for esophageal varices due to idiopathic portal hypertension following systemic lupus erythematosus (in Japanese). Jpn J Clin Immunol 2004;27:40–7.
8. Yasuda E, Kurisu Y, Sumiyoshi K, Akutagawa H, Kurokawa T, Takeshita A, et al. A case of rheumatoid arthritis and systemic lupus erythematosus with portopulmonary hypertension (in Japanese). Kanzo 2003;44:465–70.
9. Takahashi C, Kumagai S, Tsubata R, Sorachi K-I, Ozaki S-I, Imura H, et al. Portal hypertension associated with anticardiolipin antibodies in a case of systemic lupus erythematosus. Lupus 1995;4:232–5.
10. Adachi Y, Sugiyama T, Ogawa A, Suga M, Yabana T, Yachi A, et al. A case of idiopathic portal hypertension associated with systemic lupus erythematosus (in Japanese). Jpn J Gastroenterol 1993;90:2951–5.
11. Suzuki A, Takashina N, Okada J, Kondo H, Ohbu M, Kashiwazaki S. A case of systemic lupus erythematosus associated with idiopathic portal hypertension (in Japanese). Jpn J Clin Immunol 1989;12:668–74.
12. Takagi K, Ashida H, Ishikawa Y, Utsunomiya J. A case of idiopathic portal hypertension associated with SLE (in Japanese). Kanzo 1988;29:938–41.
13. Kato M, Noma K, Takeuchi Y, Nagano M. A case of idiopathic portal hypertension supervening on SLE (systemic lupus erythematosus) – a study on the possible role of SLE in the pathogenesis of IPH- (in Japanese). J Jpn Soc Intern Med 1986;75:1836–40.
14. Hasui H, Uchida T, Yagasaki M, Hayashi S, Shikata T. A case of SLE associated with idiopathic portal hypertension and pulmonary hypertension (in Japanese). Kanzo 1986;27:383–9.
15. Ohbu M, Yamamoto K, Okudaira M. An autopsy case of idiopathic portal hypertension associated with systemic lupus erythematosus (in Japanese). In: Okuda K, editor. Report of the Research Committee on Idiopathic Portal Hypertension of Ministry of Health and Welfare 1983. Tokyo: Japan Ministry of Health and Welfare; 1984. p. 33–9.

16. Sekiguchi Y, Amano K, Takano Y, Saito K, Itoh I, Tsuzuka K, et al. Portal and pulmonary hypertension in a patient with MCTD (in Japanese). Ryumachi 1999;39:657–63.
17. Iijima H, Enomoto K, Nishigami T, Shimomura S, Amuro Y, Hada T, et al. Spontaneous regression of focal nodular hyperplasia of the liver in a case of mixed connective tissue disease with idiopathic portal hypertension (in Japanese). J PHEV 1998;4:416–20.
18. Ozawa T, Nakagawa O, Hasegawa S, Honda T, Kikuchi M, Sato T, et al. A case of mixed connective tissue disease accompanied with idiopathic portal hypertension and pulmonary hypertension (in Japanese). J Jpn Soc Intern Med 1989;78:1799–1800.
19. Muryoi T, Harata N, Tamate E, Sasaki T, Yoshinaga K. A case of mixed connective tissue disease with idiopathic portal hypertension (in Japanese). J Jpn Soc Intern Med 1989;78:984–5.
20. Sawaki T, Tsuchikawa K, Watanabe T, Kyogoku M. A case of mixed connective tissue disease (MCTD) complicating pulmonary hypertension and portal hypertension (in Japanese). Ryumachi 1988;28:164–9.
21. Horiie H, Seto K, Inoo M, Kurozumi Y, Nakamura H, Akashi Y, et al. A case of primary Sjogren syndrome associated with idiopathic portal hypertension (in Japanese). Kagawaken Naikaikai Zasshi 1996;32:119–22.
22. Ueta H, Okazaki K, Ido E, Sakamoto Y, Morita M, Miyazaki M, et al. A case of intrahepatic saccular portal vein aneurysm (S-PVA) associated with Sjogren syndrome, distal renal tubular acidosis (D-RTA) and idiopathic portal hypertension (IPH) (in Japanese). Kanzo 1987;28:250–7.
23. Tsuneyama K, Harada K, Katayanagi K, Watanabe K, Kurumaya H, Minato H, et al. Overlap of idiopathic portal hypertension and scleroderma: report of two autopsy cases and a review of literature. J Gastroenterol Hepatol 2002;17:217–23.
24. Watanabe Y, Mizukami T, Egawa T, Okamoto S, Sakauchi M, Takita T, et al. A case of progressive systemic sclerosis complicated by idiopathic portal hypertension with severe anemia (in Japanese). Ryumachi 1999;39:586–90.
25. Tajima H, Inoue O, Furukawa R, Satoh A, Mine M, Fukuda T, et al. A case of progressive systemic sclerosis complicated with esophageal varix (in Japanese). J Jpn Soc Intern Med 1985;74: 1108–11.
26. Yoshimoto J, Iwata T, Kojima K, Fukasawa M, Beppu T, Futagawa S. A case of Felty's syndrome with portal hypertension (in Japanese). Jpn J Clin Surg 1998;59:790–4.
27. Handa Y, Nakajima K, Hasejima N, Kobayashi A, Suzuki T, Takezawa N, et al. A case of RA associated with idiopathic portal hypertension (in Japanese). Nisseki Igaku 1990;42:37–8.
28. Hashimoto K, Yamamoto R, Shibayama Y, Nakata K, Wada M. Idiopathic portal hypertension following viral hepatitis (B) and rheumatoid arthritis: Report of an autopsy case (in Japanese). Kanzo 1989;30:492–5.
29. Kakei K, Mozai T, Isoda K, Mori H, Nakata K. Idiopathic portal hypertension (IPH) accompanied with chronic rheumatoid arthritis: report of an autopsy case (in Japanese). Kanzo 1987;28:617–22.
30. Sama SK, Bhargava S, Gopi Nath N, Talwar JR, Nayak NC, Tandon BN, et al. Noncirrhotic portal fibrosis. Am J Med 1971;51:160–9.
31. Mikkelsen W, Edmondson H, Peters R, Redeker A, Reynolds T. Extra- and intrahepatic portal hypertension without cirrhosis (hepatoportal sclerosis). Ann Surg 1965;162:602–20.
32. Okuda K, Obata H. Idiopathic portal hypertension (Hepatoportal sclerosis). In: Okuda K, Benhamou JP, editors. Portal hypertension. Berlin Heidelberg New York Tokyo: Springer; 1991. p. 271–87.
33. Fukasawa M, Futagawa S. The changes and present condition on the concept of idiopathic portal hypertension (in Japanese). Kanzo 2000;41:5–15.
34. Fujimoto A. Criteria of idiopathic thrombocytopenic purpura (1990) (in Japanese). In: Nomura T, editor. Report of the Research Committee on idiopathic dyshemopoiesis of Ministry of Health and Welfare 1990. Tokyo: Japan Ministry of Health and Welfare; 1991. p. 59–61.
35. Rosenstein ED, Kramer N. Felty's and pseudo-Felty's syndrome. Semin Arthritis Rheum 1991;21:129–42.
36. Ohta G, Saito K, Nakanuma Y. A survey of idiopathic portal hypertension (IPH) associated with autoimmune phenomena (in Japanese). In: Okuda K, editor. Report of the Research Committee on Idiopathic Portal Hypertension of Ministry of Health and Welfare 1983. Tokyo: Japan Ministry of Health and Welfare; 1984. p. 176–9.