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Polyarteritis Nodosa of the Gallbladder (A Report of Two Cases)†

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= **Abstract** = This report describes two cases of polyarteritis nodosa presenting as cholelithiasis for which cholecystectomy was performed. Clinically one (case 2) was totally asymptomatic, while the other (case 1) suggested the multisystem involvement of polyarteritis nodosa.

In both cases, HBsAg in serum was negative and investigation on the affected arteries by PAP method with anti-HBsAg antibody revealed no significant results. Relationship between polyarteritis nodosa and cholelithiasis was discussed.

Key words: ***Polyarteritis nodosa, Vasculitis, Cholelithiasis, Gallbladder***

INTRODUCTION

Polyarteritis nodosa is generally known as a multisystem disorder, being characterized by vasculitis of small and medium-sized arteries with fibrinoid necrosis and irregular, often segmental destruction of the internal elastic membrane leading to aneurysm formation (LiVolsi *et al.* 1973). The more usual sites of involvement are the kidney, heart, liver and gastrointestinal tract in descending order, followed by the pancreas, testis, skeletal muscle, nervous system and skin (Robbins *et al.* 1984). Even with the rarity of this condition, there are several cases of polyarteritis nodosa of single organ involvement, including gallbladder in which the association of cholelithiasis is little discussed along with the mechanism (Goldner and Wainfeld 1960; Schwartz *et al.* 1966; Remigio and Zaino 1970; LiVolsi *et al.* 1973; Suh 1986; Kim 1986). This paper reports two cases in which the diagnosis of polyarteritis nodosa was made by examination of the surgically removed gallbladders with cholelithiasis.

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CASE REPORT

Case 1

A fifty years old female was brought to the Seoul National University Hospital emergency unit because of fever, chills, anorexia and nausea. About one month prior to admission, red urine as well as fever, myalgia, malaise, and oliguria developed and she was given some medicine, with which her urine amount returned to normal. She was managed with antituberculous drugs for four days at another local clinic, but thereafter she complained severe nausea. On admission she was acutely ill looking, but alert. Blood pressure was 130/70 mmHg and body temperature was 37°C. Abdomen was slightly distended with rebound tenderness in her right upper quadrant and decreased bowel sounds. No organs or masses were palpated. Initial laboratory findings were as follows; urinalysis revealed WBC 15-20/HPF, RBC 1-2/HPF and epithelial cells 7-10/HPF. SGOT/SGPT were 47/42 IU/ml. After fourteen days, urinary findings and liver function tests returned to normal. Serum albumin was lower than normal range (2.8gm). ESR was 87mm/hr. ASO, CRP and RA factors were positive and HBsAg/HBsAb were −/+. VDRL and AFB on sputum were negative. Electrocardiography showed first degree AV block. Ultrasonography of the gallbladder revealed multiple stones. Cholecys-

tectomy was done at the 11th hospital day. No intraabdominal abnormalities were detected elsewhere. Postoperative course was uneventful.

Pathologic findings: The gallbladder measured 7 cm in length and 3cm in maximum width. Serosa was smooth but showed finely nodular thickening of the wall, whereas the mucosa appeared velvety without erosion. There were multiple star-shaped black pigment stones measuring up to 1cm. Microscopically almost every medium-sized and small artery in the muscular and serosal layers showed various stages of arteritis, some of which were characterized by infiltration of lymphocytes, eosinophils and plasma cells around the typical fibrinoid necrosis of the vascular wall. Occassionally obliterative arteritis due to marked intimal edema and thrombosis with disruption of the vessel wall was noted. Elastic fiber staining revealed segmental disruption of the internal elastic lamina. This was associated with a mild chronic inflammatory cell infiltration in the lamina propria of the gallbladder wall. Immunoperoxidase stainings with anti-HBsAg antibody and anti-IgG antibody were all negative.

Case 2

A seventy years old male was referred to the Seoul National University Hospital because of a known gallstones which were noted on ultrasonography at another hospital. He complained of weight loss of 4 Kg and abdominal distention for 5 months. Past medical history included subtotal gastrectomy because of gastric ulcer 7 years ago. On physical examination, blood pressure was 90/70 mmHg and the previous operation scar was noted on the anterior abdominal wall. No mass was palpated. Laboratory findings were within normal limit except high cholesterol level (235 IU/l). Serum HBsAg was negative and blood eosinophilia was absent. Radiologic examination of the lung showed diffuse increase in interstitial markings on both lower lung fields and an old calcification on the right upper lung. Upper gastrointestinal series revealed no barium passage disturbance. On abdominal ultrasonography, the gallbladder was septated, filled with multiple stones and slightly thickened. Under the impression of cholelithiasis, a cholecystectomy was done.

Pathologic findings: The gallbladder measured 9×3×2cm in maximum dimension and disclosed congested serosa and partially eroded mucosa. It contained six bright yellow multifaceted stones, ranging from 0.5×0.5×0.3cm to 0.2×0.2×0.2 cm. Microscopically, the mucosa was the seat of diffuse goblet cell and pyloric glandular metaplasia and lymphoid cell infiltration with scattered follicle formation. Serosa was edematous, showing moderate lymphatic dilatation and multifocal vasculitis. The vasculitis mainly involved small arteries, manifested by moderately heavy infiltration of neutrophils, lymphocytes and eosinophils together with complete disruption of vascular walls and luminal occlusion. A few foci of adjacent venous involvement were noted. A piece of liver tissue obtained during the operation showed mild portal inflammation, however parenchymal damage was absent.

DISCUSSION

Vascular changes of the gallbladders in both cases are characterized by a necrotizing vasculitis of small and medium-sized muscular arteries. Many clinical syndromes of vasculitis are classified on the basis of the size of blood vessels involved, tissue or organ affected, stage of inflammation, and morphological features of the lesion (Lasser and Ghofrany 1976). Absence of granulomas or giant cells distinguishes these cases from allergic granulomatosis and Wegener's granulomatosis. Hypersensitivity vasculitis involves neither muscular arteries nor venules and are all in same stage. In giant cell arteritis, fibrinoid necrosis is absent and presence of giant cells is characteristic. The involvement of the adjacent venules to the affected arteries in case 2 is rarely described in polyarteritis nodosa (Zeek 1952).

Based on histological staging of arterial changes in polyarteritis nodosa, the vasculitic features in both cases are classical for the active stage (I and II) of polyarteritis nodosa. Absence of infarctive necrosis is explained by rich anastomosing vascular supply of the gallbladder.

Eosinophils, characteristically noted in inflammatory infiltrates of polyarteritis nodosa as in our two cases, have been once said to be a classical finding and customarily regarded as an aid in distinguishing polyarteritis nodosa from other overlap subgroups. Nightingale (1959) reported 220 cases of polyarteritis nodosa with gastrointestinal complications, of which 34.6% revealed blood eosinophilia. Rose and Spencer (1957) found a significant eosinophilia mostly in patients with lung involvement in 10 of 14 cases. However, a study of 30 autopsy cases revealed that neither cases with complica-

tions secondary to small intestinal lesions such as free perforation, nor 3 cases with a previous cholecystectomy and proved acute arteritis of the gallbladder had any eosinophilia. Thus blood eosinophilia is uncommon and not characteristic, and can not be correlated with any particular organ localization of polyarteritis nodosa (Patalano and Somers 1961).

Aneurysmal dilatation of medium-sized arteries is one of the characteristic features of polyarteritis nodosa, however the femoral angiography in case 1 revealed no aneurysmal dilatation of hepatic or renal arteries.

Polyarteritis nodosa may present protean clinical manifestations as a multisystem disorder and usually involves the kidney, heart, liver and gastrointestinal tract simultaneously or asynchronously (LiVolsi *et al.* 1973). Common clinical manifestations of polyarteritis nodosa are such nonspecific systemic reactions as fever, malaise, weakness, leukocytosis and symptoms reflecting the degree and location of vessel involvement (Fauci *et al.* 1978). Nightingale (1959) reviewed 220 cases of polyarteritis nodosa in which 36 (16%) had gastrointestinal symptoms as presenting complaints. Although pathologic involvement of the gallbladder is generally regarded as a frequent finding at autopsy (Owano and Sueper 1966), the clinical presentation of polyarteritis simulating acute cholecystitis or association with cholelithiasis has been rarely reported in English literature. (Goldner and Wainfeld 1960; Schwartz *et al.* 1966; Bohrod and Bodon 1970; Dillard and Block 1970; Remigio and Zaino 1970; LiVolsi *et al.* 1973). Though nonspecific, case 1 presented symptoms such as fever, myalgia and malaise compatible with the common symptomatology of polyarteritis nodosa. In particular, urinary abnormality (red urine) may suggest renal involvement, and the initial laboratory findings also support transient renal manifestation. In contrast, case 2 revealed asymptomatic gallstones with mild weight loss only.

While the etiology of polyarteritis nodosa is still uncertain, the association with hepatitis B viral infection, rheumatoid arthritis, or systemic lupus erythematosus has been recently focused (Gocke *et al.* 1970). A particular attention, however, should be given to a case of polyarteritis nodosa without obvious causes especially in Korea where the HBsAg positivity in general population is very high; otherwise it can be easily overlooked as a nonspecific inflammatory response or masked by secondary reaction to the gallstones.

Based on the facts that HBsAg/HBsAb immune complex was demonstrated by immunofluorescent study on vessel wall (Baker *et al.* 1972) and that PAP staining with anti-HBsAg antibody in hepatitis B associated immune complex nephropathy becomes available on paraffin embedded tissue (Kim *et al.* 1986), the possibility of participation of HBsAg-related immunological injury on the vascular structures of the gallbladders were investigated, but no significant results were obtained in both cases. This negative result may be explained by the absence of persistent hepatitis B surface antigenemia, according to a study that the development of glomerular injury in Hepatitis B virus associated nephropathy required a condition of hepatitis B surface antigen excess in serum.

Acute cholecystitis is caused by cholelithiasis in 90-95% of cases. Other causes of obstruction include anomalies, edema, tumors, blood clots and echinococcal cyst. Vascular factors such a thrombosis of the cystic artery and polyarteritis nodosa can play a role in the development of acute cholecystitis (Andersson *et al.* 1971). A possibility of secondary lithiasis following the mucosal change by inflammatory extention of polyarteritis nodosa in the subserosa can be raised, but the extent of vasculitis remained only outside the mucosa and activity of vasculitis is not corresponding to the mucosal changes required for nidus formation. Thus, the association of polyarteritis nodosa and cholelithiasis in both cases may reflect just no more than chance occurrence. The histopathologic changes of metaplastic mucosa in case 2 are the common features in cholelithiasis as in chronic cholecystitis (Yu *et al.* 1984).

It is questionable whether the arteritis in the gallbladder wall represents a localized phenomenon or a manifestation of a generalized disease. Multisystemic clinical symptoms such as hematuria may stress the latter possibility in case 1. Although the clinical course after cholecystectomy was uneventful with treatment of steroid and aspirin, a close follow-up is mandatory to exclude the subsequent development of other systemic manifestations.

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=국문초록=

담낭의 다발성 결절성 동맥염
—2례보고—

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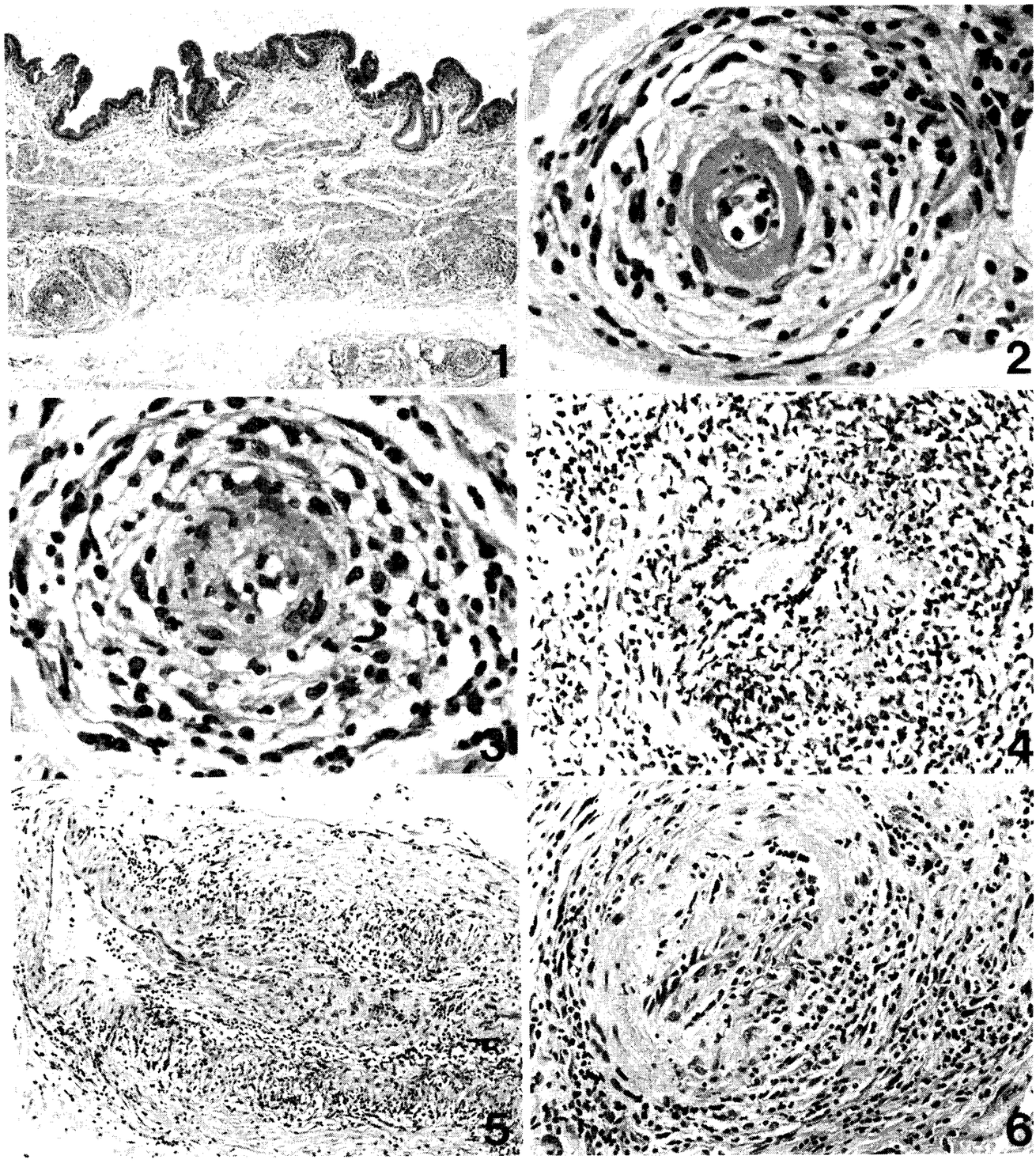
유은실 · 김용일

우리나라에서 관찰되는(전신성) 교원질환중 다발성 동맥염의 발생은 극히 드물며 특히 담낭을 포함한 단일 장기 침범을 시사하는 증례는 문헌상 제한되어 있다. 저자들은 55세 여자환자 및 70세 남자환자에서 담석이 의심되어 절제한 담낭에서 전형적인 다발성 결절성 동맥염의 소견을 보인 2예를 보고하는 바이다.

제1증례는 일시적인 간기능 검사의 이상, 근육통 및 혈뇨의 임상증상을 보여 다른 장기를 침범했을 가능성을 배제할 수 없었으나 제2증례는 담낭염 증상만을 보여 고립성 병변으로 사료되었다.

또한 동맥염의 원인으로 대두되어 있는 B형 간염바이러스 간염과의 연관성을 알아보고자 B형 간염표면항원에 대한 PAP 염색을 시행하였으나 두 증례 모두 음성이었다. 두 증례에서의 담석증의 수반은 본 동맥염과 무관하다고 사료되었다.



LEGENDS FOR FIGURES

Fig. 1. Diffuse involvement of vasculitis of small and medium-sized arteries in the gallbladder wall. Case 1 (H&E, x40)
Fig. 2. Circumferential fibrinoid necrosis of intima with perivascular cuffing of lymphocytes. Case 1 (H&E, x400)
Fig. 3. Obliterative arteritis by fibrinoid necrosis and endovasculitis. Case 1 (H&E, x400)
Fig. 4. Intense exudative reaction in the background of fibrinoid necrosis. Case 2 (H&E, x200)
Fig. 5. Destruction of elastic membrane and media with incipient phase of aneurysm formation. Case 2 (H&E, x200)
Fig. 6. Segmental destruction of elastic lamina by inflammatory infiltrates. The upper portion of the wall is relatively preserved. Case 2 (H&E, x200)