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Case report

Gastric plasmacytoma and multisystem autoimmune disease

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Summary. A 54-year-old women with solitary gastric plasmacytoma, Ig M and kappa-light chain type, associated with multisystem autoimmune disease is described. The gastric plasmacytoma developed seven years after the diagnosis of Hashimoto's thyroiditis, primary biliary cirrhosis and Sjögren's syndrome. We speculate that this plasmacytoma developed in association with an immunodeficient and/or immunosuppresed state resulting from multisystem autoimmune disease and therapy.

Key words: Autoimmune disease – Gastric plasmacytoma – Hashimoto's thyroiditis – Primary biliary cirrhosis – Sjögren's syndrome

Introduction

Autoimmune diseases have often been associated with malignant tumors. Up to 20% of all cases of dermatomyositis appear to combine malignancy (Calobro 1967). In patients with such diseases, immunosuppressants are usually used and may also induce the progression of neoplasms, particularly lymphoma (Penn 1978). To our knowlege, an association of solitary plasmacytoma and multisystem autoimmune disease has not reported. We describe a case of gastric plasmacytoma associated with Hashimoto's thyroiditis, primary biliary cirrhosis and Sjögren's syndrome, and discuss the pathogenetical relationship between them.

Case report

A 54-year-old woman was admitted to our hospital for the second time in February, 1982, because of a suspected gastric tumor.

She had a ten-year history of Raynaud's phenomenon and an episode of drug allergy for mefenamic acid. She had been admitted for the first time in June, 1975, because of general malaise, myxoedema of the face and lower extremities, slow speech, impaired hearing, enlarge-

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ment of the right lobe of the thyroid and hepato-splenomegaly. Liver function tests revealed elevated values of alkaline phosphatase (Al-Pase) 1050 U/l (normal 35–55), serum glutamic oxaloacetic transaminase (SGOT) 209 U/l (10–37) and serum glutamic pyruvic transaminase (SGPT) 135 U/l (5–47). There was a hyperproteinemia [total protein 8.8 g/dl (6.4–7.9), albumin 36.5% (62.9–73.7), gamma-globulin 40.2% (8.7–17.7), Ig G 1900 mg/dl (802–1556), Ig A 280 mg/dl (130–367), Ig M 660 mg/dl (55–189)] and hypercholesteremia [total cholesterol 564 mg/dl (115–211)]. Thyroid function tests revealed Resind-T_3 uptake (RT_3U) 19.1% (25–35) and serum thyroxine (T_4) 2.1 g/dl (5.0–13.7). Microsome antibody was 1:400 (1:100↓) and the Rose Bengal test was slightly positive. Antinuclear factor, rheumatoid factor and thyroglobulin antibody were all negative. An open biopsy of the thyroid gland was performed on June 28, 1975, needle biopsy of the liver on July 17 and biopsy of a labial salvary gland on July 23. Diagnoses of Hashimoto's thyroiditis, chronic hepatitis and Sjögren's syndrome were made.

She was discharged on September 2, 1975 and treated as an outpatient with dessicated thyroid (total, 30 mg for 5 months), levothyroxin natrium (50 mg for 2 years), prednisolone (4000 mg for 5 months), methylprednisolone (10 g for 5 years), and azathioprine (130 g for 5 years) until January, 1982.

She complained of the left hypochondralgia after fasting in October, 1981. The roentgenological and endoscopic examinations revealed a submucosal tumor of the stomach. Thus, she was admitted for further examination and therapy in February, 1982. Physical examination revealed several xanthomas of the face and chest and abscence of all the teeth. Main laboratory data were as follows; Al-Pase 543 U/l, SGOT 97 U/l, SGPT 96 U/l, total cholesterol 271 mg/dl, total protein 5.5 g/dl, albumin 55.3%, gamma-globulin 15.8%, Ig G 960 mg/dl, Ig A 174 mg/dl, Ig M 266 mg/dl, white cell count 7200/mm^3 with 74% neutrophils, 31% lymphocytes, 2% monocytes and 2% eosinophils. Immunological examinations were as follows: T cell 92% (60–80) and B cell 1% (8–16) in the peripheral blood; T helper cell (OKT-4)/T suppressor cell (OKT-8) 0.6 (2.0 ± 0.3); antimitochondrial antibody 1:80 (1:10↓). Skin reactions for testing delayed hypersensivity were negative with phytohemagglutinin (PHA), dinitrochlorbenzene (DNCB) and purified protein derivative (PPD). A biopsy of the labial salivary gland was done on February 26. Biopsy of the sternal and iliac bone exhibited a markedly hypocellular marrow, in which there was neither an increase in number of plasma cell nor infitration of atypical cells. A subtotal gastroectomy with gastrojejunostomy and a wedge biopsy of the liver were performed on April 15, 1982. She was discharged on June 18, 1982. There is no recurrence of the plasmacytoma for 20 months.

Materials and methods

Light microscopy. The resected stomach and all biopsy specimens were fixed in 10% formalin and embedded in paraffin. Sections were stained with haematoxylin and eosin, Gimesa, periodic acid Shiff and silver impregnation.

Electron microscopy. Small blocks of the gastric tumor were fixed in phosphate-buffered 2.5% glutaraldehyde (pH 7.4) for 2 h, and postfixed with phosphate-buffered 1% osmium tetroxide for 1 h. Blocks were dehydrated in graded series of ethanol and embedded in epoxy resin. Ultrasections were doubly stained with uranyl acetate and lead citrate, and examined with a Hitachi HU-12 electron microscope.

Immunoperoxidase study. 4 μm thick sections of the gastric tumor and the thyroid gland were deparaffinized, and processed with rabbit anti-human sera (Ig G, Ig A, Ig M, kappa and lambda, Dako, Denmark), goat anti-rabbit Ig G antibody (Tago, USA) and rabbit peroxidase-antiperoxidase complex (Dako), according to the unlabeled antibody peroxidase-antiperoxidase method (Sternberger et al. 1970). Endogenous peroxidase activity was blocked by incubating the sections in a 3% hydrogen peroxidas solution. Counterstaining was done with methyl-green.

Pathological findings

Thyroid gland. Follicles in the biopsy material were difficult to recognize because of notable infiltrates of lymphocytes with germinal centers and plasma cells (Fig. 1). Remnants of thyroid follicles and epithelial nests persisted, often with granular acidophilic cytoplasm (Hürthle cells).

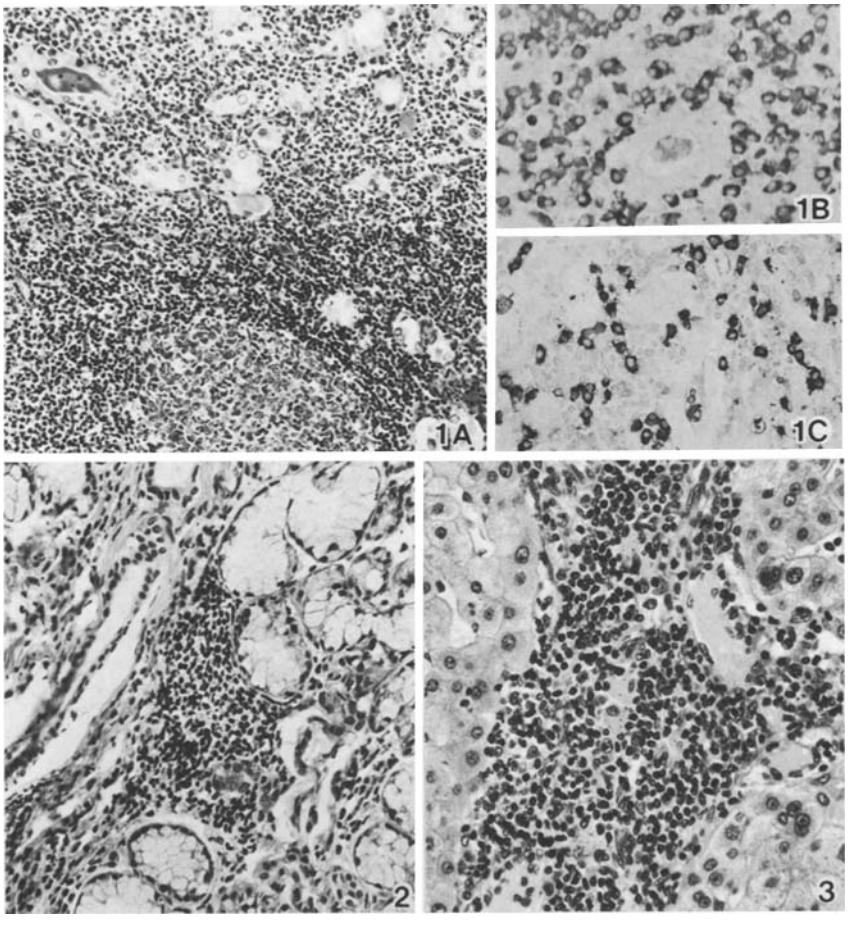

Fig. 1 A–C. Biopsy of the thyroid gland showing marked infiltrates of lymphocytes and plasma cells, a germinal center and oxyphilic change of follicular epithelium (**A**, Haematoxylin and eosin, ×130). Infiltration of Ig G- (**B**) and Ig M- (**C**) positive plasma cells (PAP method, ×120)

Fig. 2. Biopsy of the salivary gland showing a focal lymphocytic infiltrate in the portal periductal area. Haematoxylin and eosin, ×170

Fig. 3. Biopsy of the liver showing marked infiltrates of inflammatory cells, consisting of lymphocytes, plasma cells and macrophages, and dilatation of the portal tract. Haematoxylin and eosin, ×230

Immunohistochemically, the approximate ratio of immunoglubulin-positive cells for kappa and lambda light chain was 3:2, and that of Ig G:Ig A:Ig M was 55:10:15 (Fig. 1 B and C).

Labial salivary glands. The first biopsy, taken in 1975, revealed focal lymphocytic sialadenitis (Fig. 2) of grade 3 according to Chisholms's grading system for Sjögren's syndrome (1968). The second, taken in 1982, showed interstitial fibrosis, atrophy of the acinar cell and no lymphocytic infiltration.

Liver. The first needle biopsy, taken in 1975, revealed infiltrates of lymphocytes and slight fibrosis in portal tracts. Piecemeal necrosis was found in the interface between the connective

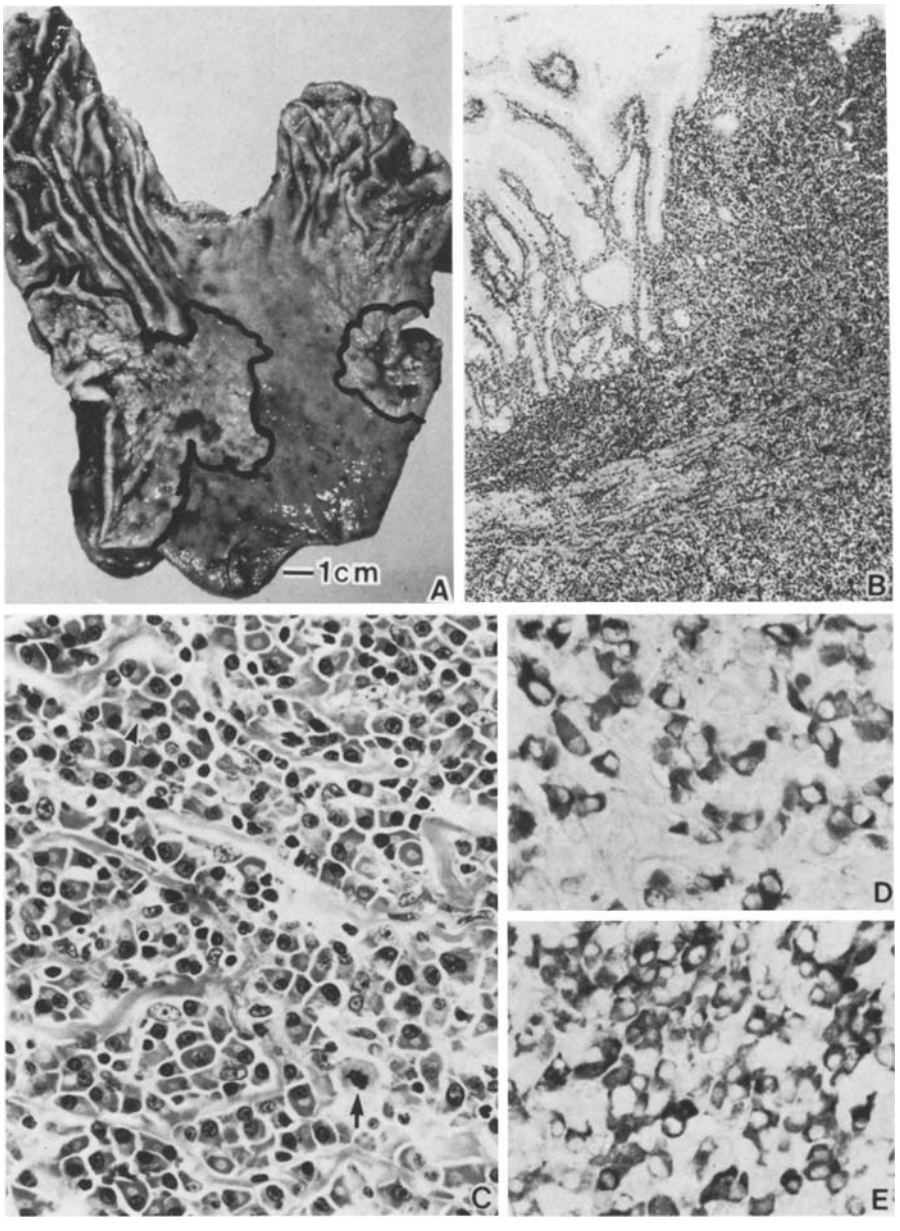

Fig. 4A–E. Resection of the stomach. Gross photograph showing a elevated lesion with small ulcers, and solid line enclosing the extent of the tumour (**A**). Lower power view of the tumour showing a massive infiltrate of plasma cells from the lamina propria to the submucosa (**B**, Haematoxylin and eosin, ×52). High power view showing relatively differentiated plasma cells. Note binucleated cell (*arrowhead*) and mitotic figure (*arrow*) (**C**, Haematoxylin and eosin, ×340). Neoplastic plasma cells are stained with Ig M (**D**) and kappa light chain (**E**) (**D** and **E**, PAP method, ×400)

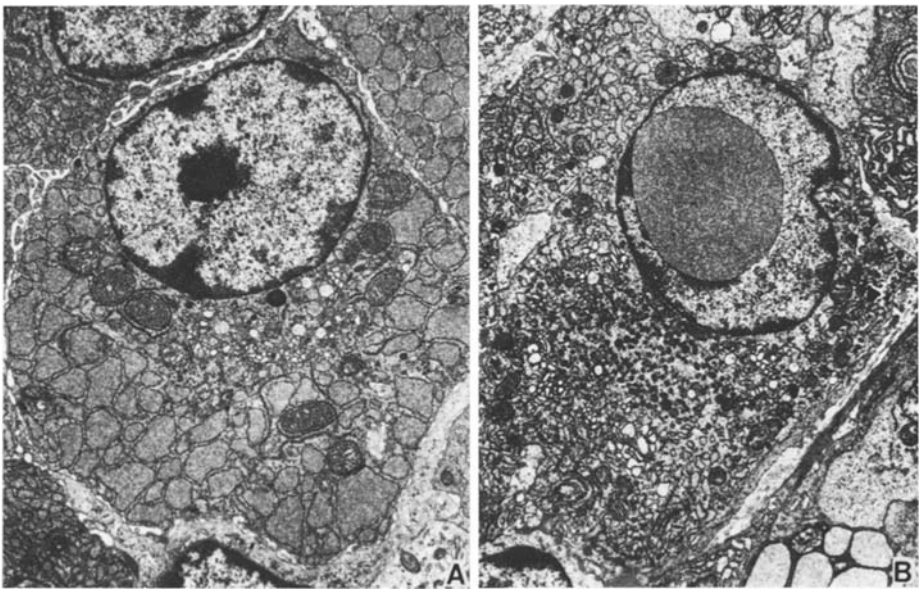

Fig. 5A, B. Electron micrographs showing abundant rough endoplasmic reticulum with occasionally dilated cisterna and prominent Golgi apparatus (**A**, ×4,800). Most of the nuclei show a small quantity of heterochromatin and have large nucleoli and an occasional nuclear inclusion (**B**, ×4,800)

tissue and the parenchyma. The second wedge biopsy, taken in 1982, revealed moderate infiltrates of inflammatory cells, composed of lymphocytes, plasma cells and bile-pigment-laden macrophages, in portal tracts, and compressed features of small bile ducts (Fig. 3). A diagnosis of stage I primary biliary cirrhosis was made according to MacSween's classification (1979). Retrospectively, the pathohistological feature of the first biopsy specimen, diagnosed as chronic hepatitis, seemed to have been an early change of primary biliary cirrhosis.

Stomach. The subtotally resected stomach, measuring 23 cm along the greater curvature and 11 cm along the lessure, had a 9×9 cm, irregular-shaped, and slightly elevated lesion of the body on the anterior and posterior walls with a few, small and shallow ulcers (Fig. 4A). On the cut-sections, the gastric wall of the elevated lesion showed thickening and induration. Histologically, the elevated lesion revealed a dense and diffuse proliferation of plasma cells from the lamina mucosa to the submucosa (Fig. 4B). The plasma cells consisted of mature and immature types, and had basophilic cytoplasm, usually eccentric unclei and "cartwheel" arrangement of nuclear chromatin, showing moderate pleomorphism (Fig. 4C). Some plasma cells had binucleated nuclei and prominent nucleoli. Mitoses were rare. No neoplastic plasma cells were present in the two lymph nodes attached to the greater omentum. The neoplastic cells contained intracytoplasmic Ig M/k (Fig. 4D and E). A few plasma cells contained Ig G, Ig A and lambda light chain in the cytoplasm.

Electron microscopically, the cytoplasm of neoplastic cells had a large amount of rough endoplasmic reticulum, occasional dilated cisternae, prominent Golgi apparatus and a few mitochondria (Fig. 5A). Most of nuclei were large, and the characteristic clock-face pattern was apparant in some of them, but the heterochromatin pattern was scanty. Large globular intranuclear inclusions were found in some nuclei (Fig. 5B).

Discussion

Although more than sixty-six cases of primary gastric plasmacytoma have been reported, only 5 cases have immunohistological descriptions (Habe-

shaw et al. 1975; Scott et al. 1978; Nakanishi et al. 1982). According to their reports, intracytoplasmic immunoglobulin was of Ig G/k type in two cases, Ig A/k in one, Ig G/l in one, and the coexistence of Ig A/l, Ig G/l and Ig G/k in one. However, Seo et al. (1982) reported that nine out of 18 primary gastric lymphoma cases were of B-cell origin, demonstrating Ig M/k in 5 cases, Ig G/k in two, Ig G/l in one and Ig A/k in one as intracytoplasmic immunoglobulin. Thus, intracytoplasmic immunoglobulin of Ig M/k has not been reported in cases of solitary extramedullary plasmacytoma consisting of pure plasma cells. This type of immunoglobulin was identified in extra-salivary malignant lymphoma associated with Sjögren's syndrome (Schmid et al. 1982).

Knecht et al. (1981) examined immunoglobulin-containing cells in the thyroid of Hashimoto's thyroiditis immunohistochemically, and showed that the ratio of immunoglobulin-positive cells for Ig G, Ig A and Ig M was 80:10:1. Our data from the biopsy specimen for the thyroid in this case were 55:10:15, and the relative component of Ig M-positive cells was increased comparing with their results. This may be related to the development of the Ig M-plasmacytoma, in other words, the variation in intracytoplasmic immunoglobulin type in the tumor cells of the present case may have been induced by the underlying autoimmune diseases.

There is an apparent relationship between the progression of tumors and a decreased or altered effectiveness of the host's immune mechanism. The incidence of malignancy in patients with primary immunodeficiency is about 10,000 times larger than that of the general age-matched population, and high proportion of these tumors are lymphomata (Gatti and Good 1971). It is reported also that patients with autoimmune diseases, especially with Sjögren's syndrome or Hashimoto's thyroiditis, have a high incidence of lymphomas (Maurer et al. 1979; Schwarze and Papadimitrious 1980; Schmid et al. 1982). However, no case of extramedullary plasmacytoma with Sjögren's syndrome or Hashimoto's thyroiditis has been reported. Only one case of gastric plasmacytoma with an immunological disorder, gluten-sensitive enteropathy, has been reported by Habeshaw et al. (1975).

Maurer et al. (1979) proposed that lymphomas associated with autoimmune diseases may represent the emergence of a malignant clone following a phase of prolonged antigenic stimulation of the immune system, and that the system may develop progressive abnormalities or be abnormal *ab initio*. The predominant incidence of B-cell lymphoma in patients with autoimmune diseases suggests a control defect of the B-cell line and/or an abnormality of T-cell helper/suppressor cell system that modulates the B-cell response. An abnormality of T-cell function is suggested by the laboratory examination in this case.

Many cases of malignant tumors have been observed in patients treated with immunosuppressive agents (Penn 1978), and a case of plasmacytoma in a renal transplant recipient has been reported (Hara et al. 1979). A large amount of the drugs were used for Hashimoto's syndrome, primary biliary cirrhosis and Sjögren's syndrome, and these immunosuppresive effects may be additional factors in the development of the plasmacytoma in this case.

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