Letters to the Editor

Coexistence of Mucosa-associated Lymphoid Tissue Lymphoma with Plasma Cell Features and Adenocarcinoma Cells in Pleural Fluid

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To the Editor

A 59-year-old man presented with accumulation of pleural fluid. As reported previously in detail, the patient first presented with gastric mucosa-associated lymphoid tissue (MALT) lymphoma eight years earlier, which responded to antibiotic therapy for the eradication of Helicobacter pylori (H. pylori). Three years before the current presentation, however, he underwent subtotal gastrectomy due to gastric perforation. The excised stomach showed transmural infiltrates of MALT lymphoma and regional lymph nodes showed the histopathology of marginal zone B-cell lymphoma. The patient was further treated with six cycles of chemotherapy consisting of rituximab, vincristine, cyclophosphamide, and prednisolone, and was subsequently lost to follow-up.

Computer-assisted tomography of the chest at this presentation revealed a large amount of pleural fluid within the left thoracic cavity. Although mediastinal adenopathy was identified, no primary tumor was apparent within the lung field. Endoscopic examination of the upper gastrointestinal tract revealed no recurrent disease at the site of anastomosis. Laboratory data included a hemoglobin level of 11.3 g/dL, white blood cell count of 8,100/μL with 7% plasmacytoid cells, and platelet count of 379,000/μL. Blood chemistry was unremarkable except for a total protein level of 8.4 g/dL and albumin of 3.6 g/dL. Protein electrophoresis revealed an M-spike, which migrated in the fast γ-globulin region; immunoelectrophoresis confirmed that monoclonal immunoglobulin (Ig) in the serum was labeled by IgA as well as IgM and α-light chain anti-sera, and the κ chain was excreted in the urine. The serum level of IgA was 1,677 mg/dL, that of IgG was 981 mg/dL, and IgM was 241 mg/dL.

Thoracentesis yielded exudative fluids containing monoclonal Ig identical to that found in the serum; the levels of Ig were 1,030 mg/dL IgA, 652 mg/dL IgG, and 132 mg/dL IgM. Cytologic examination of the fluids demonstrated lymphoplasmacytoid cells (Fig. 1A), and flow cytometry of the mononuclear cell fraction confirmed a monoclonal B-cell population with plasma cell differentiation; i.e., the cells were CD10-, CD19+, CD20-/+, CD38+, CD138-/+, and surface membrane and cytoplasmic Ig α-light chain+ (Fig. 2); the predominant heavy chain was α. On the other hand, the pleural fluid contained large clumps of atypical epithelial cells (Fig. 1A, B). Some cells showed a signet ring cell morphology (Fig. 1, inset) and were positive for periodic acid-Schiff (PAS) staining (Fig. 1C). The cells corresponded to the class V category of the cytopathological grading. Prominent values of tumor markers in the fluids included 8,540 U/mL CA19-9 and 27,500 U/mL CA125, and their serum levels were 433 U/mL CA19-9 (normal level in serum, C37U/mL) and 317.4 U/mL CA125 (C35.0 U/mL).

Cytogenetic analysis was performed after short-term culture of the pleural fluid cells. The G-banded karyotype of 6 out of 20 metaphase spreads analyzed was 46, XY, t(11;18)(q21;q21), fluorescence in situ hybridization using a kit confirming t(11;18) detected a fusion signal on the der (11) t(11;18) chromosome, corresponding to the production of the API2/MALT1 chimeric protein, and interphase cells carrying one fusion signal (Fig. 3). As the der (18) t(11;18) chromosome lacked the expected fusion signal, a part of the reciprocal MALT1/API2 fusion gene may have been deleted. On the other hand, the majority of interphase nuclei showed multiple hybridization signals; 3 green and 4 orange signals in 37% of nuclei, and 4 green and 4 orange signals in 28% of nuclei (Fig. 3).
Fig. 1. Appearance of pleural fluid cells. (A) Giemsa staining. Lymphoma cells and a clump of adenocarcinoma cells are indicated by thin arrows and a thick arrow, respectively. (B) Papanicolaou staining of adenocarcinoma cells that were present in a three-dimensional cluster. (C) FAS staining. Inset, Papanicolaou staining showing signet-ring cells. (A-C): ×100.

Fig. 2. Flow cytometry of lymphoma cells. The cells of interest were analyzed by two-color flow cytometry, using combinations of the antibodies indicated. Sm: surface membrane, c: cytoplasmic.

Fig. 3. Fluorescence in situ hybridization analysis of metaphase and interphase cells. Chromosome preparations were hybridized with the Vysis® LSI ® API2/MALT1 t(11;18)(q21; q21) dual color, dual fusion translocation probe, comprising of green-labeled API2 and orange-labeled MALT1 probe (Abbott Laboratories, Abbott Park, Illinois, USA). The der(11) t(11;18) and der(18) t(11;18) chromosomes are indicated by an arrow and an arrowhead, respectively. Two interphase nuclei containing 3 green and 4 orange signals, one nucleus containing 4 green and 4 orange signals, and two diploid nuclei are shown. Inset, An interphase cell showing the pattern of two green, one orange, and one fusion signal (arrow), which agrees with that of the metaphase cell.
It is clear that the pleural fluid contained both MALT lymphoma cells with t(11;18) and polyploid adenocarcinoma cells. The mixture of 3- and 4-green signal cells may correspond to the loss of chromosome 11q materials, which has been observed in adenocarcinoma by comparative genomic hybridization studies.\(^3,4\) Although the site of origin of the latter tumor was not determined, the prolonged clinical course of the patient suggests a link between the two tumors. \(H.\, pylori\), has been implicated in the pathogenesis of not only gastric MALT lymphoma but also in carcinoma of the stomach.\(^7\) Indeed, the two neoplasms of the stomach can develop in the same patient synchronously or metachronously, despite \(H.\, pylori\) eradication.\(^3,4\) We reviewed histological specimens of the excised stomach prepared three years earlier; however, all specimens were composed of infiltrates of lymphoid cells and no carcinomatous lesions were identified. Nevertheless, as the specimens covered only part of the entire stomach, it is possible that we had missed concurrent gastric cancer which had disseminated to finally develop malignant effusion along with MALT lymphoma. High-levels of CA19-9 and CA125 are compatible with advanced stage of gastric cancer.\(^9\)

Other important points regarding this case were the plasma cell features and the diminished CD20 expression of the MALT lymphoma cells, in contrast to those of the excised stomach and the regional lymph node of three years earlier, both of which expressed CD20.\(^1\) MALT lymphoma tissues include plasmacytoid cells with varying degrees of maturation,\(^10\) and the disease is often associated with monoclonal gammopathy,\(^11\) suggesting that MALT lymphoma cells have the potential to differentiate into the CD20- plasma cell stage. This report supports the proposal that rituximab or rituximab-containing chemotherapy may promote the differentiation and/or preferential proliferation of CD20- cells, thereby causing the disease to be resistant to the immunochemotherapy.\(^1,12\)

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REFERENCES