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Low Grade Fibromyxoid Sarcomas and Multiple Myeloma in the Same Patient: One Case Report and Literature Review

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Introduction

Multiple myeloma (MM) is a neoplastic plasma cell dyscrasia characterized by anemia; a monoclonal protein (M-protein) in the serum and/or urine; abnormal bone radiographs and bone pain; hypercalcemia; and renal insufficiency or failure. According to the results of immunoelectrophoresis, patients are separated to Ig type (IgG, IgA, IgD, IgE and IgM); light chain; nonsecretory[1].

Many kinds of second malignancies in patients with MM have been reported[2]. But low grade fibromyxoid sarcomas (LGFMS) secondary to MM has not been reported in the literature yet. We report herein an unusual case of LGFMS in a 57-year-old woman with MM and review the literature regarding LGFMS and second malignancies in patients with MM.

Case Report

This patient was a 57-year-old Chinese woman. She was diagnosed with MM (IgG light chain subtype) 5 years ago by anemia; abnormal plasma cell hyperplasia in bone marrow smear, a monoclonal IgG in the serum; bone pain and abnormal bone radiographs. According to Durie-Salmon staging[3] it was stage IIIA and based on the international staging system (ISS) staging[4] it was stage III. This patient received 30 Gy radiation at manubrium sterni and the right fifth posterior segment of rib to relieve the bone pain at the beginning of the disease. She then received 23 cycles of chemotherapy regimens including: VAD (vindesine + epirubicin + dexamethasone); VMCP (vinorelbine + melphalan + cyclophosphamide + prednisone); MP (melphalan + prednisone); and BADT (bortezomib, thalidomide, epirubicin and dexamethasone). The cumulative doses of melphalan and cyclophosphamide were 624 mg and 5.6 g, respectively. She achieved complete remission (CR) after a single cycle of BADT treatment presenting normal bone marrow plasma cell count and negative M-protein by immunofixation electrophoresis. But she began to feel chest distress and breathlessness and gradually deteriorated. Physi-

cal examination exposed satiation of the right compartments of the thorax, dull percussion note of the right lung, vanishing of respiratory sound of right lung, and enlargement of heart boundary. Chest X-ray and CT scan showed surrounding soft tissue mass of manubrium sterni and the right fifth and sixth posterior segment of ribs, right large volume pleural effusion with floating mass (Fig.1). We conducted thoracentesis for the patient. The pleural effusion was bloody, adenosine deaminase 9 μ/L, LDH 1032 μ/L, protein 41 g/L, WBC 370 × 10^6/L, lymphocyte 58%, neutrophil 18%, macrophage 21%, mesothelial cell 3%, immunofixation electrophoresis was negative, bacterium, fungus and acid-fast bacilli culture, and acid-fast staining were all negative. No tumor cells were identified in concentrated pleural effusion. We conducted another course of BADT treatment, meanwhile conducting intracavitary injection of CTX twice a week, and bortezomib twice a week. The patient' s situation didn't improve. So we did a blind biopsy of pleural membrane while conducting thoracic drainage. This patient died of respiratory failure 2 days after this biopsy.

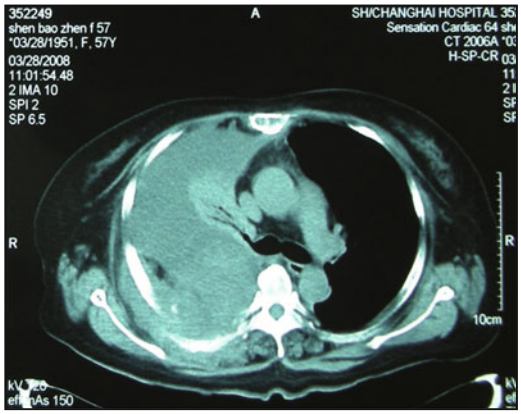

Fig.1. Images when the patient felt chest distress and breathlessness. CT scan showed surrounding soft tissue mass of manubrium sterni and the right fifth and sixth posterior segment of ribs, right large volume pleural effussion with floating mass.

Light microscopy and immunohistochemistry

Three pieces of pleural tissue about 2 × 2 cm^2 were removed. Histologic sections were routinely processed and stained with hematoxylin-eosin. Immunohistochemistry for smooth muscle actin (SMA), S-100, CD34, CD68, cytokeratin, vimentin, epithelial membrane antigen (EMA), Lysozyme, Calponin, mesothelial cell antigen (MCA), Rhabdomyosarcoma Marker (MyoD1), D2-40 (to label mainly lymphatic endothelium), Myogenin, Desmin, Calbindin, MUM1 (multiple myeloma 1/interferon regulatory factor 4) and Ki-67 was performed on formalin-fixed paraffin-embedded sections. Antigen recovery was enhanced using heat-induced epitope retrieval in which the sections were placed in a citrate buffer solution (pH 6.1) for 25 min at 94°C to 99°C using a vegetable steamer. Immunostaining was performed using an automated immunostaining system (Dako Autostainer Universal Staining System; Dako, Carpinteria, CA) with primary antibody incubations of 30 min at room temperature. Appropriate positive and negative tissue control slides were used.

Histopathology

Microscopic examination of the pleural tissue showed an admixture of hypocellular myxoid and hypercellular spindle cell areas. There was abrupt transition from hypocellular to hypercellular areas in which the spindle cells formed an indistinct storiform or whorled pattern. In other areas, spindle cells were arranged in a fascicular pattern. Sheets of anaplastic cells were seen. The vasculature was obvious in only a minority of sections and consisted predominately of open and compressed, sometimes branching arteriole-sized vessels with a few arcades of smaller vessels (Fig.2A).

Immunophenotype

Immunohistology showed diffuse strong positive staining of spindle cells with vimentin (Fig.2B) and focal positive staining with SMA, Calponin. Ki-67 was (++). No staining was observed with CD34, CD68, cytokeratin, S-100, EMA, Lysozyme, MCA, MyoD1, D2-40, Myogenin, Desmin, Calbindin, MUM1.

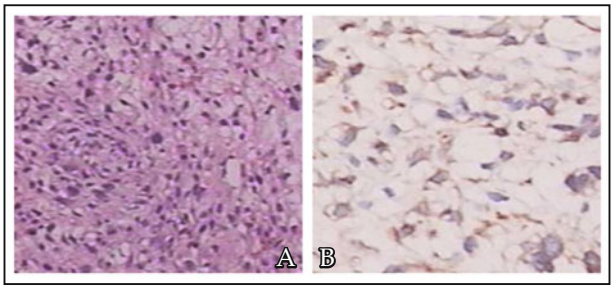

Fig.2. Histopathology and immunohistochemistry of the biopsy tissue from pleural membrane. A, The spindle cells formed an indistinct storiform or whorled pattern (10 × 10); B, Immunohistology showed diffuse strong positive staining of spindle cells with vimentin (10 × 40).

Discussion

This patient had been diagnosed with MM for 5 years. After repeated chemotherapy, the MM was well controlled. Especially after one cycle of bortezomib based treatment, the normal bone marrow plasma cell and negative M-protein by blood and urine immunofixation electrophoresis indicated the CR of MM. The negative immunofixation of pleural fluid also excluded the likelihood of pleural plasmacytoma. At last the biopsy of pleural mass confirmed the bloody hydrothorax was due to LGFMS.

LGFMS are indolent but potentially metastasizing soft tissue tumors, which were reported first by Evans et

al. and Devaney et al.[5-7]. These fibroblastic tumors typically occur in the lower limb/groin area but sporadically occur in other deep soft tissue. Of the people recorded to have had LGFMs, males and females are represented equally. Their ages range from 6 to 51 years, but most are young adults. The microscopic appearance of LGFMS is consisting of bland fibroblasts with a whorled or linear arrangement, alternating with less cellular areas with a myxoid stroma. Tumor cells tend to be small, and poorly defined. Mitotic figures tend to be absent to sparse. Sheets of anaplastic cells were seen in 10% cases, which was similar to intermediate-grade fibrosarcoma. Immunohistochemical staining showed positive staining with vimentin, indicating fibroblastic differentiation. Focal muscle specific actin positive staining, which attributes to focal myofibroblastic differentiation. Immunoreactivity to desmin, and cytokeratin has been seen in occasional cases. Recurrent and specific genetic abnormalities involving t(7;16) (q33;p11) that results in a fusion of the FUS and CREB3L2 genes appear unique to this neoplasm[8-11]. In LGFMS a long hiatus (≥ 10 years) is common before the appearance of metastatic disease. But it has often developed local recurrence after resection and resistant to chemotherapy and radiation[12].

Primary intrathoracic LGFMS is very rare. The 6 reported primary intrathoracic LGFMS all occurred in adults (mean, 39 years; range, 20-50 years). Three of these occurred in the anterior mediastinum[13-15], 1 in the pleura[16], and 2 from within the lungs[17,18]. Our case is the first reported patient with LGFMS secondary to MM and the sarcomas occurred in pleura, which is not a site that was previously considered likely for LGFMS. Though LGFMS is indolent and usually has a long survival time. This patient died quickly after the occurrence of the bloody hydrothorax. One explanation is the respiratory failure resulting from bloody hydrothorax due to intrathoracic sarcoma. Another explanation is the sheets of anaplastic cells seen in a pathological slice, which indicated a relatively aggressive clinical process.

Second malignancies in patients with MM have been frequently reported in the past 40 years, among them leukemia is most common[19,20]. The incidence of leukemia in patients with MM is 0.7%-25%, which is 100-200 times higher than in the general population[21,22]. It is well known that administration of melphalan to patients with MM increases the likelihood of leukemia and it seems possible that the advanced stage of MM is more vulnerable to the leukaemogenic effect of melphalan compared with the earlier stages. Other alkylating agents, such as cyclophosphamide can also cause therapy-related leukemia[4]. Lymphoma in patients with MM was also reported. Ohnishi H et al. encountered a 65-year-old woman with diffuse large B-cell lymphoma that developed following 12 years of melphalan-based chemotherapy and radiation for MM[23].

Solid tumors secondary to MM were sporadically reported, including lung cancer, hepatoma, bladder carcinoma and adenocarcinoma of the colon, glioblastoma, prostate adenocarcinoma, breast carcinoma, endometrial carcinoma, and soft tissue sarcoma[24-29]. In a retrospective analysis of a series of 210 patients with myeloma, solid malignancies were observed in 6.2% of patients with myeloma and occured at an advanced stage, IgG myelomas predominated in early stages. In most cases the solid malignancies were diagnosed in advanced stages. A short-term high mortality rate was observed due to progression of the solid malignancy [30]. Another evaluation in 628 consecutive patients with multiple myeloma who had been treated with various melphalan-prednisone combinations showed the incidence and diversity of second tumors were similar to those in normal persons of the same age and duration at risk. The diagnosis was usually made within 2 years after the start of chemotherapy for the myeloma[31].

This patient had a long duration of chemotherapy for MM before LGFMS occurred. She had received high-dose alkylating agents and anthracycline agents. The cumulative doses of melphalan and cyclophosphamide were 624 mg and 5.6 g respectively. The DNA damage induced by chemotherapeutic agents, especially alkylating agents, may be an important cause of the onset of LGFMS.

Radiation is another potential cause of secondary malignancies. Vukmirović et al.[25] described a patient with a rare combination of primary and secondary malignant bone tumors. The primary bone tumor was histologically established as myeloma, and was treated by radiation and multiple-drug chemotherapy. The secondary tumor, histologically confirmed 19 years later, was osteogenic sarcoma occurring in the radiation field when clinical and laboratory examinations showed remission of the primary lesion[26].

In this patient, the localization of the second tumor is the same as the primary plasmacytoma and the radiation field at the fifth right posterior segment of the rib, and the latent period of elapsed years, indicates that the secondary tumor may have been induced by irradiation.

Alhough the secondary malignancies were likely to have been induced by the treatment of the first primary cancer (chemotherapy, radiotherapy), common etiologies, misclassification, or progression of the initial cancer cannot be ruled out entirely. The observation of Bacha et al. supported the hypothesis that Kaposi's sarcoma and multiple myeloma share a common etiology such as Human Herpes Virus 8[32].

Conflict of interest statement

No potential conflicts of interest were disclosed.

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