CASE REPORT

Interleukin-6-producing Thymic Squamous Cell Carcinoma Associated with Castleman’s Disease and Nephrotic Syndrome

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Abstract

When a 63-year-old man was hospitalized with nephrotic syndrome due to focal segmental glomerulosclerosis, a mediastinal mass was discovered. A biopsy specimen obtained by mediastinoscopy showed findings compatible with the plasma cell type of Castleman’s disease. Fever, anemia, and anti-nuclear antibody were present. Serum concentrations of gamma globulin, acute phase proteins, and, most strikingly, interleukin-6 (IL-6) were elevated. Methylprednisolone pulse therapy resulted in no clinical improvement. Pathologic examination of the resected thymic tumor showed a squamous cell carcinoma immunoreactive for IL-6. To our knowledge, this case represents the first reported IL-6-producing thymic squamous cell carcinoma associated with Castleman’s disease and nephrotic syndrome.

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Key words: mediastinal tumor, focal segmental glomerulosclerosis

Introduction

Interleukin-6 (IL-6) is a multifunctional cytokine acting mainly in the initiation of acute inflammatory responses and induction of B lymphocyte proliferation and differentiation (1). This cytokine is produced by a variety of cells such as T cells, B cells, monocytes, fibroblasts, keratinocytes, astrocytes, and mesangial cells (1, 2). Several human tumors or lymphoproliferative lesions also secrete IL-6, including multiple myeloma (3), renal cell carcinoma (4), lung cancer (5), cervical cancer (6), esophageal cancer (7), and Castleman’s disease (8). Furthermore, the serum IL-6 concentration is correlated with disease status and prognosis in esophageal squamous cell carcinoma (7).

Thymic carcinoma is a rare mediastinal cancer. This tumor displays notable cytologic atypia in the neoplastic epithelial component of the thymus and is likely to invade adjoining tissue and metastasize (9). Among thymic carcinomas, squamous cell carcinoma is the most common and ordinarily is of relatively low grade histologically (10). Whether or not thymic squamous cell carcinomas produce IL-6 has not been established. We treated a patient with both thymic carcinoma and the plasma cell type of Castleman’s disease who exhibited high serum concentrations of IL-6, as well as focal segmental glomerulosclerosis with nephrotic syndrome. To our knowledge, this case represents the first instance of such an association.

Case Report

A 63-year-old man was admitted to our hospital in January 1999 because of edema and general malaise. Three months before admission, he noted edema in his legs and a gain in weight from 64 to 74 kg. He had no history of proteinuria. Physical examination revealed anasarca with massive ascites. No peripheral lymphadenopathy was present.

On admission, laboratory results included: red blood cells, 304×10^4/μl; hemoglobin 9.3 g/dl; hematocrit, 28.3%; white blood cells, 14,800/μl (neutrophils 77%, eosinophils 3%, basophils 0%, lymphocytes 12%, monocytes 8%); platelets, 27.2×10^4/μl; serum albumin, 0.9 g/dl; blood urea nitrogen, 20.6 mg/dl; serum creatinine, 1.4 mg/dl; and C-reactive protein, 3.1 mg/dl. An antinuclear antibody test was positive (1:1,280, speckled pattern). The Wassermann reaction, complement studies, rheumatoid factor, and assays for immune complexes and anti-neutrophil cytoplasmic antibody showed normal results.

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Matsumura et al

mg/dl), but no monoclonal band was present either in serum or in urine. A 24-h urine collection contained 29.7 g of protein. The urinary sediment contained 10 to 19 red blood cells per high-power field and 2 to 3 granular casts per low-power field. The creatinine clearance was 35.7 ml/min. Serum and urinary concentrations of IL-6 were 44.3 pg/ml (normal, <4.0) and 14.8 ng/day (normal, <5.0), respectively. A chest roentgenogram obtained upon admission showed a large, well-demarcated mass overlying the right hilum (Fig. 1). Computed tomography of the thorax revealed a large, low-density anterior mediastinal mass measuring 6 by 5 by 7 cm and projecting laterally (Fig. 2). The mass showed a weak enhancement upon contrast medium administration.

Percutaneous renal biopsy was performed on the second hospital day. Light microscopic findings indicated focal segmental glomerulosclerosis (Fig. 3). After radiologic screening

Figure 1. Frontal radiograph of the chest showing a large mass in the right upper mediastinum.

Figure 2. Computed tomographic scan showing weakly enhanced tumor in the anterior mediastinum.

Figure 3. A glomerulus showing a segmental sclerosis and hypertrophic glomerular epithelial cells (periodic acid-Schiff stain, x250).

Figure 4. Biopsy specimen obtained from anterior mediastinal tumor showing proliferation of mature-appearing plasma cells in the interfollicular zones (HE stain, top x100, bottom x330).
for potential sources of metastases, the tumor was biopsied during mediastinoscopy on the 38th hospital day. The biopsy specimens were composed of lymphoid tissue exhibiting hyperplasia of lymphoid follicles with prominent germinal centers and marked capillary proliferation. Interfollicular zones contained sheets of mature-appearing plasma cells (Fig. 4). No lymphoepithelial lesion, hyalinized vessels or malignant cells were noted. Plasma cell type of Castleman’s disease was diagnosed.

The patient initially withheld consent for operation, thus methylprednisolone pulse therapy (1 g/day for 3 days) was given three times for nephrotic syndrome, followed by oral prednisolone (40 mg/day). The treatment was partially effective, decreasing proteinuria to 5 g/day. However, the mass increased in size, serum concentrations of IL-6 rose to 78.9 pg/ml, and white blood cells increased to 26,800/μl. A low-grade fever persisted. The patient underwent tumor resection in July 1999. Serum concentrations of IL-6 decreased to 16.6 pg/ml after surgery, but exceeded the normal value. Leukocytosis over 20,000/μl persisted. One month later the patient developed right hemiplegia as a result of brain metastasis and died in October 1999. No autopsy was performed.

The tumor was located in the anterior mediastinum and compressed the superior vena cava and innominate veins, but did not invade the lungs or pulmonary vessels. Grossly, the tumor was well-circumscribed and measured 8 by 7 by 6.6 cm. Microscopically, the tumor represented a proliferation of atypical squamous cells (Fig. 5). Single-cell keratinization and apoptotic cells were occasionally observed. No intercellular bridges were identified. Necrotic foci were numerous. Clusters of plasma cells and lymphocytes were scattered within the tumor. Sheets of plasma cells as seen in the biopsy specimen still were present in mediastinal lymph nodes to which the squamous cell carcinoma had metastasized. Immunohistochemical staining was performed in formalin-fixed, paraffin-embedded sections. Avidin-biotin complex method (DAKO LSAB+ Kit, CA) was used with the following antibodies: goat polyclonal antibodies to human IL-6 (DAKO), 1:100; anti-immunoglobulin lambda light chain monoclonal antibody (DAKO), 1:3,000; anti-immunoglobulin kappa light chain monoclonal antibody (DAKO), 1:3,000. The sections for IL-6 staining were pretreated by microwave exposure for 15 minutes. The color reaction was developed with a 3,3′-diaminobenzidine-peroxide substrate. Meyer’s hematoxylin was used for counterstaining. Immunoreactivity for IL-6 was detected in the cytoplasm of cancer cells (Fig. 6). A number of plasma cells also were immunoreactive for IL-6 and showed cytoplasmic expression of polyclonal immunoglobulin light chains.

**Discussion**

The present case was the first to be described where an IL-6-producing thymic squamous cell carcinoma coexisted with the plasma cell type of Castleman’s disease. The patient also had focal segmental glomerulosclerosis with steroid-resistant nephrotic syndrome. He died of brain metastasis from the thymic squamous cell carcinoma.

Various human tumors produce IL-6 (4–7), including some squamous cell carcinomas (6, 7). Previous studies demonstrated elevation of IL-6 in serum and tumor cell cytoplasmic immunostaining for this cytokine in patients with squamous cell carcinomas arising in skin (2), uterine cervix (6), and esophagus (7). In addition, Yoshizaki et al (8) reported a patient with Castleman’s disease who showed a decrease in serum IL-6 following surgical removal of the involved lymph nodes. The present patient continued to have high serum concentrations of IL-6 after resection of the tumor and mediastinal lymph nodes, and ultimately developed brain metastasis. Although other hyperplastic lymph nodes involved by Castleman’s disease might have been present as a source of IL-6 in serum, we note a report from Ikeda et al (11) of thymic squamous cell carcinoma producing and secreting this cytokine, as have been described in other squamous cell carcinomas.
been reported previously, we suspect that IL-6 may have been a useful serum marker for metastasis or recurrence of thymic squamous cell carcinoma.

Nephrotic syndrome was the presenting symptom in the present patient. Renal complications of Castleman’s disease are uncommon; approximately 40 cases have been reported (12–14). A variety of renal diseases have been represented including renal amyloidosis, interstitial nephritis, mesangial proliferative glomerulonephritis, and membranoproliferative glomerulonephritis (12–14). However, focal segmental glomerulosclerosis was found in only one previously reported patient (14). On the other hand, there is no reported case of coexisting thymic carcinoma and nephrotic syndrome. In our previous studies concerning urinary IL-6 excretion in a variety of glomerulonephritides, no significant association was observed with patients with focal segmental glomerulosclerosis (15, 16). Although causal relationships and mechanisms remain unknown, our patient was interesting in terms of the potential association of thymic carcinoma and/or Castleman’s disease with focal segmental glomerulosclerosis.

The patient had shown persistent leukocytosis until death. Leukocytosis is not uncommon in the plasma cell type of Castleman’s disease (17, 18) and we administered corticosteroid to the patient. Nevertheless we can not exclude the possibility that the tumor might secrete granulocyte colony stimulating factor which is known to be produced by squamous cell carcinomas of various organs (19, 20). We therefore suspect that thymic squamous cell carcinoma and Castleman’s disease had coexisted at presentation. Lack of squamous cell carcinoma in the biopsy specimen may be caused by sampling error.

IL-6 is considered to play an important role in the pathogenesis of Castleman’s disease and to be closely associated with lymphoid hyperplasia (8, 21). Hypergammaglobulinemia, increased concentrations of acute phase proteins, and various clinical abnormalities are observed in that disease (8). In our patient, biopsy specimen findings and clinical features were compatible with the plasma cell type of Castleman’s disease, where capillaries do not necessarily show hyaline thickening (22). Thymic squamous cell carcinoma was diagnosed upon examination of the resected tumor. While the combination of Castleman’s disease and squamous cell carcinoma have never been reported previously, we suspect that IL-6 may have been an important pathogenetic link in this patient.

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