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Intrathoracic Castleman disease

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Aim: To analyze patients with Castleman disease who were diagnosed by surgery.

Materials and methods: We retrospectively investigated the postoperative pathological records of operations performed between January 1992 and December 2012 in our hospital. Files of 19 patients with the diagnosis of Castleman disease were analyzed.

Results: There were 13 male and 6 female patients with a mean age of 40.1 ± 11.4 (range: 20–57) years. Fifteen thoracotomies and 3 video-assisted thoracoscopies, 12 on the right side and 6 on the left side, and 1 mediastinoscopy were performed. Biopsies and mass excisions were performed in 2 and 17 cases, respectively. Histopathological findings were hyaline vascular-type (n = 16), plasma cellular-type (n = 2), and hyaline vascular plus plasma cellular-type (n = 1) Castleman disease.

Conclusion: Castleman disease can occur in all areas of the thorax, but the mediastinum and hilum are the most common locations. Surgical excision is the best method of diagnosis and treatment. Complete excision is curative for local forms of the disease. However, complete excision may not be possible at all times due to local invasion and hypervascularization. Multimodal treatment, including chemotherapy, is recommended in patients with a multicentric form of the disease, and they should be followed closely.

Key words: Castleman disease, mediastinum, lung, surgery

1. Introduction

Castleman disease (CD) is a benign lymphoid disease with varying clinical presentations (1). In 1954, Dr Benjamin Castleman, a pathologist, first described the rare lymphoproliferative disorder that now bears his name (2), and in 1956, he reported the first case series (3). CD is also termed angiofollicular lymph node hyperplasia, angiomatous lymphoid hyperplasia, Castleman tumor, giant benign lymphoma, lymph node hamartoma, and giant lymph node hyperplasia (4). The prevalence of CD has not been established; it is estimated that this disease affects fewer than 200,000 people in the United States (1). It can be observed in various age groups, from adolescence to individuals in their 70s. It is clinically classified into localized and multicentric types, and histopathologically as hyaline vascular, plasma cellular, and mixed types of CD (4–6).

CD can be observed in any part of the body. It was reported that 70% of lesions are located in the thorax, 15% in the neck, and 15% in the abdomen and pelvis (1). In this study, we present patients with Castleman disease located in thorax who underwent surgery.

2. Materials and methods

Postoperative pathology results of patients who were operated on in our surgical department during 1992–2012 were retrospectively examined. Data were analyzed for 19 patients diagnosed with Castleman disease. Demographic characteristics, clinical presentations, diagnostic methods, surgical data, histopathological results, postoperative treatments, prognoses, morbidity, and mortality were evaluated.

All of the patients underwent chest radiography, routine blood tests, respiratory function test, and thorax computed tomography (CT) before surgery.

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3. Results

Of the 19 patients, 13 were male and 6 were female. Mean age was 40.1 ± 11.4 years (range: 20–57 years). Fourteen patients were symptomatic, while 5 were asymptomatic and accidentally diagnosed from chest radiography. Symptoms included chest pain (n = 8), coughing (n = 3), shortness of breath (n = 1), shortness of breath combined with loss of weight (n = 1), and dysphagia and loss of weight (n = 1). Physical examinations were normal. Patients' past histories included bulla ligation surgery 12 years previously, pneumonia 4 years previously, tube thoracostomy due to pneumothorax 5 months previously, and prostate carcinoma at the time of diagnosis.

Routine laboratory tests showed hemogram and biochemistry parameters within normal limits. Lesions were identified in the pathologic presentation of chest radiography for all patients. Thorax CT analysis found solid lesions between 2 and 12 cm (mean: 5.8 cm). Lesions were located on the mediastinum in 11 cases (3 anterior, 8 posterior mediastinum), the hilum in 7 cases (Figure 1), and the lungs and mediastinum in 1 case (Figures 2A and 2B). In 1 patient, the left superior pulmonary vein passed to the mediastinum at the left hilar level and followed a vertical course. Three-dimensional CT analysis found that the left superior pulmonary vein poured into the left brachiocephalic vein. Echocardiography of this patient with a partial pulmonary venous return abnormality showed no cardiac pathology. Due to a suspicion of pulmonary malignancy, abdominal ultrasonography, brain CT, and bone scintigraphy were conducted in 9 patients, while positron emission tomography (PET) was done in 4 patients. No extrathoracic pathology was detected in patients, with the exception of 1 patient who was examined at another center for prostate cancer; in that patient, PET showed activity retention in the posterior mediastinum (standard uptake value max: 3.6) apart from the prostate. The PET of 1 patient showed involvement in the bilateral lungs as well as the supraclavicular and mediastinal lymph nodes. A supraclavicular lymph node biopsy taken from this patient was evaluated as sinusoidal histiocyte proliferation at a different center. Fiberoptic bronchoscopy analysis of patients found no bronchial system pathology other than a narrowing of the upper lobe bronchus with exterior pressure. Only the patient with bilateral lung lesions underwent transthoracic fine-needle biopsy for diagnostic purposes, but it was not diagnostic. Other patients did not undergo biopsies, as the location of the lesions was not appropriate. Two patients underwent endobronchial ultrasonographies, which were not diagnostic. Two patients had gastroesophagoscopies due to lesions neighboring the esophagus. Gastroesophageal reflux was detected in 1 patient, while Barrett's esophagus was detected in another. All patients over 40 years of age were examined by the internal medicine department, while those over 50 were examined by the cardiology department and approval was obtained for surgery.

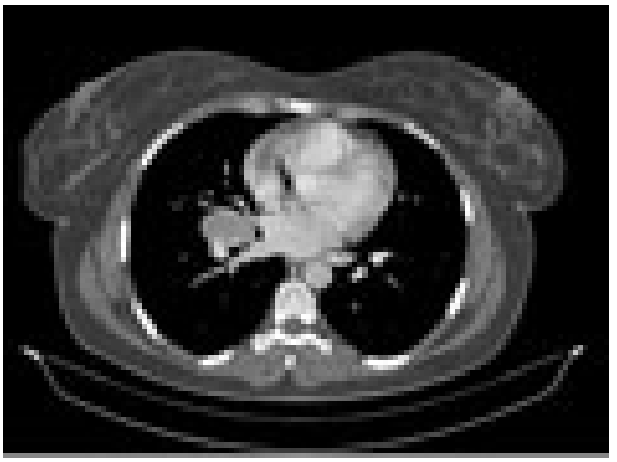

Figure 1. Thorax CT appearance of the lesion localized in the right hilar region.

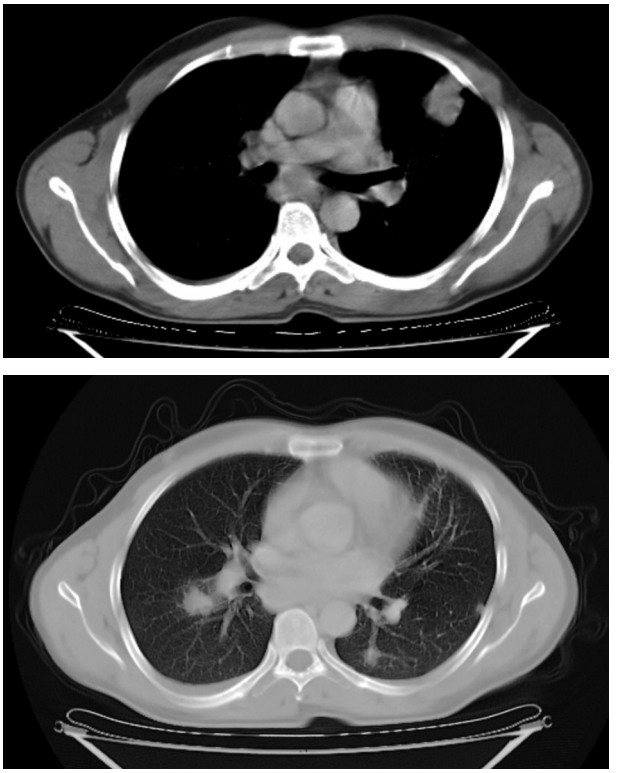

Figure 2. A) Thorax CT appearance of multicentric plasma cellular CD that involves the lung and mediastinal lymph nodes (mediastinum window). **B)** In the same patient, thorax CT appearance of bilateral multiple pulmonary lesions (lung window and different image).

No patients had a preoperative histopathological diagnosis. Surgery was performed for both diagnosis and treatment. Fifteen patients underwent thoracotomies (11

right, 4 left); 3 underwent video-assisted thoracoscopies (1 right, 2 left). One patient had a mediastinoscopy but, due to bleeding during the operation, the procedure was changed to a median sternotomy. Lesions were located in the posterior mediastinum in 5 patients, in the hilum in 3 patients, in the anterior mediastinum in 3 patients, pulmonary in 2 patients, intercostal in 2 patients, lymph node number 11 in 2 patients, pulmonary and lymph node number 7 in 1 patient, and multiple lymph nodes in 1 patient. Three patients underwent pulmonary wedge resections; 1 of them additionally had a lymphadenectomy; 1 patient had a lymph node biopsy; all other patients had mass excisions. No additional procedure was performed since intraoperative frozen pathological analysis showed that the lesions were not malignant. Complete resection was achieved in 15 of the patients. However, complete resection could not be achieved in 2 cases (R2): in 1 patient due to excessive bleeding of lesions and excessive adherence of lesions to the esophagus wall involving the posterior mediastinum, and in 1 patient due to the location of the lesion on the superior and median pulmonary veins. Two patients had multicentric CD and diagnostic biopsies. Postoperative histopathological analysis showed that 16 of the lesions were hyaline vascular (Figure 3), 2 were plasma cellular (Figures 4A and B), and 1 was hyaline vascular and plasma cellular mixed-type CD involving lung and mediastinal lymph nodes.

All patients without postoperative complications were referred to the oncology clinic. Two patients had a multicentric and the others had a localized form of the disease. The human herpes virus 8 (HHV-8) DNA relationship was analyzed in 3 patients; the results were not positive. Follow-up periods of patients varied between 2 months and 21 years. The patient with mixed-type lung involvement was given 6 postoperative courses of rituximab treatment. This patient was followed with no problems for 1 year. The patient who was diagnosed via biopsy was given corticosteroid treatment by the medical oncology clinic, but this treatment was not effective and chemotherapy was initiated at postoperative month 6. One of the patients who underwent R2 resection received postoperative radiotherapy; this patient was followed for 4 months after surgery without any recurrence. A second patient was followed by medical oncology without any treatment. Three patients were lost to follow-up. Other patients were followed with no problems.

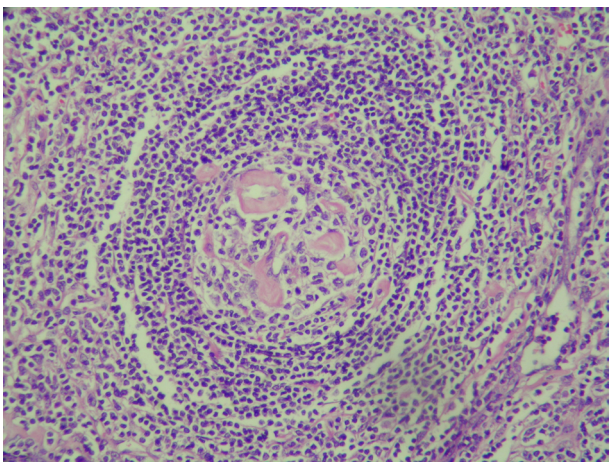

Figure 3. Hyaline vascular-type CD; the germinal center is seen with well-developed hyaline vascular structures (H&E, 400×).

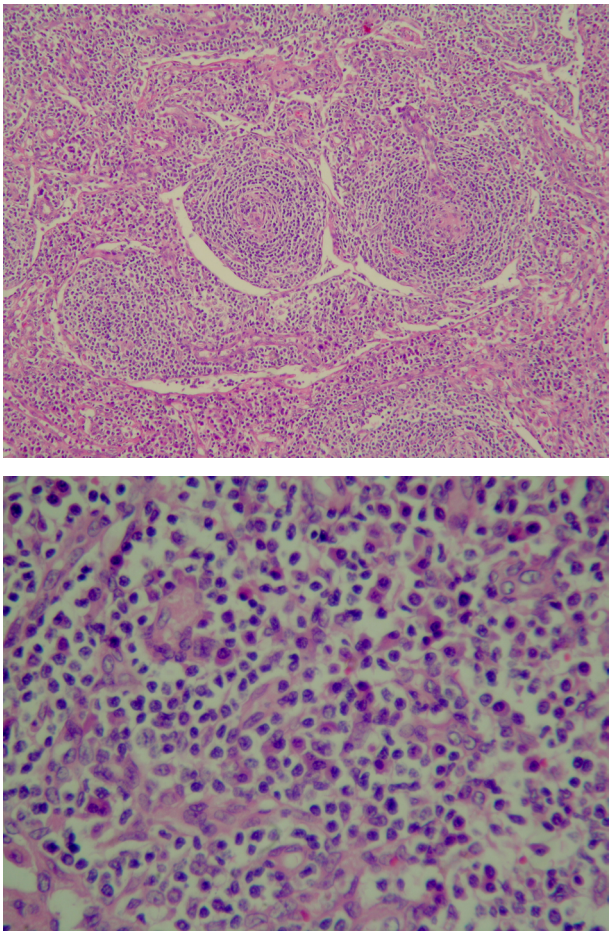

Figure 4. A) Plasma cellular-type CD. Follicular hyperplasia areas without hyaline vascular changes are observed under low magnification (H&E, 100×). **B)** Massive plasma cell infiltration is seen in the interfollicular area under high magnification (H&E, 400×).

4. Discussion

CD is angiofollicular lymph node hyperplasia caused by the abnormal proliferation of plasma cells and B lymphocytes in lymphoid tissues, and it is a rare lymphoproliferative disorder (6). Clinically, there are localized types, in which only a group of lymph nodes are involved, and a mixed type,

involving 2 or more lymph nodes. Histopathologically, there are hyaline vascular, plasma cellular, and mixed types (1). According to the histopathogenetic classification preferred in recent pathological publications, the categories are hyaline vascular CD, plasma cellular CD, HHV-8-associated CD, and multicentric CD not otherwise specified (7).

The precise etiology of CD is unknown. However, the high incidence of prior infection by opportunistic HHV-8 in immunosuppressed patients detected with CD, particularly in recent years, suggested the hypothesis that viral interleukin-6 secreted by this virus might have a role in its etiology (1,5). HHV-8-associated CD is generally multicentric and has the risk of large B cell lymphoma progression. It was reported that patients with human immunodeficiency virus (HIV)-positive CD are always infected with HHV-8 (8). Danon et al. reported that the hyaline vascular type is composed of antigen-secreting lymph nodes consisting of plasmacytoid monocytes, while the plasma cell type might develop secondary to chronic infections. However, no bacteria or other organisms were isolated (9). In our study, HHV-8 DNA was analyzed in 3 patients: 2 with plasma cell CD and 1 with mixed-type CD. None of the results were positive.

CD is more common in males (66%). The disease is very rare in children; the hyaline vascular type is mostly seen in the third and fourth decades, and the plasma cellular type in the sixth decade (10). Our series did not include pediatric patients. Patients ranged from 20 to 57 years of age. The average age of patients with the hyaline vascular type was 38.9 years, and those with the plasma cell type were 53 on average. The patient with mixed-type multicentric involvement was 33 years old.

Approximately 90% of patients have hyaline vascular CD and 90% are localized types. Rarely, cases can be multicentric or aggressive (5). Although it is asymptomatic, symptoms such as pain due to pressure, coughing, shortness of breath, dysphagia, or stridor occasionally develop (6). Plasma cell CD accounts for less than 10% of cases. Although it is mostly observed in multicentric form, prior studies have reported that it was localized in 9%–24% of cases. In plasma cellular CD, systemic symptoms and organomegaly associated with interleukin-6 levels are more prevalent. Fever, night sweats, weakness, loss of weight, anemia, thrombocytopenia, hypergammaglobulinemia, and splenomegaly might develop (5–7). HHV-8-related CD is a plasmablastic variant of CD and continues to have a poor prognosis. It generally appears in immune-suppressed and HIV-positive patients, and lymphadenopathy, structural symptoms, and hematologic and/or immunologic disorders often develop (5). Our patient group was diagnosed with 84.2% hyaline vascular, 10.5% plasma cellular, and 5.2% mixed-type CD. The lesions were multicentric in 2 patients and localized in the others. All hyaline vascular types were of the localized form. However, 1 of the plasma cellular type patients had the localized form. One of the with multicentric localization patients had the plasma cellular type while the other had the mixed type. The most common symptom was chest pain. As a systemic symptom, loss of weight was observed in 2 patients with the multicentric mixed-type CD and the hyaline vascular-type CD neighboring the esophagus.

It is difficult to diagnose CD, particularly in asymptomatic patients. In radiological terms, typical thoracic CD is generally observed in the mediastinal and hilar regions, and in the form of a round solitary mass. Mediastinal CD might be confused with thymoma, lymphoma, sarcoma, hemangiopericytoma, or neurogenic tumors. Hilar CD can be confused with lung cancer. It is rarely located in pleural, pericardial, intercostal, and intrapulmonary areas (5,10,11). Thorax CT scans identified 3 presentations for the localized form of the disease: solitary noninvasive masses were most prevalent (50%), followed by infiltrative masses accompanied by lymphadenopathy (40%) and lymphadenopathy with no masses (10%). Homogeneous intensive contrast involvement and hypervascular lesions are characteristic. It was reported that calcification might be observed in 5%–10% of patients. On the other hand, multicentric lesions can typically be observed in the form of bilateral hilar and mediastinal lymphadenopathy, centrilobular nodular opacity, and rarely ground glass, consolidation, and bronchiectasis (10,12). The value of PET in diagnosis is disputed, as it is not able to distinguish between malignant disease and CD. However, it is beneficial to show pathological involvement for a surgical approach and in terms of whole-body scans (13). In our study, in terms of tomography, lesions were most commonly mediastinal and then hilar. Only 1 patient had bilateral lung lesions and mediastinal lymphadenopathy. However, in the postoperative period, some mediastinal and hilar lesions were found in intrapulmonary (n = 2), intercostal (n = 2), and interlobar (n = 2) locations.

In patients radiologically diagnosed with hypervascular lesions, if surgery is decided upon, preoperative embolization is recommended to lower the risk of excessive bleeding (6,14). In our study, none of the patients diagnosed with hypervascular lesions underwent preoperative embolization. One patient experienced excessive bleeding.

As in our study, since CD cannot be distinguished from benign and malignant lesions, generally no preoperative diagnosis is reached. An accepted approach for both diagnostic and therapeutic reasons is surgical excision of these lesions (15). The patients who underwent surgical excision showed that surgery is almost always curative for

either the hyaline vascular type or plasma cell localized CD (8,10,16). Due to the invasive nature of lymphadenopathy in multicentric diseases, complete surgical excision is rarely possible (17). While surgical approaches typically involve posterolateral thoracotomy, the literature contains a limited body of research on video-assisted thoracoscopic resection (8). The mode of surgical approach in our study mostly involved standard thoracotomy (78%) and video-assisted thoracoscopy (15%). Mass excision was performed in all but 2 patients. Curative resection was also achieved in all but 2 localized cases.

Surgery provides excellent prognosis for the localized form of the hyaline vascular type of CD. Radiotherapy is recommended in localized patients who cannot be resected or for whom complete resection cannot be applied. Response to radiotherapy was reported as 72% (18). In multicentric or aggressive forms, steroids, and/or systemic chemotherapy, and in final stages rituximab, are recommended when necessary (19). Plasma cellular CD has a worse prognosis than hyaline vascular CD and a better prognosis than HHV-8-related CD. Single or combined chemotherapy, immune modulators (such as interferon alpha and thalidomide), monoclonal antibodies (such as anti-interleukin-6 and anti-CD20), and antiviral drugs are used to treat the multicentric form of CD (5,10). In our study, 1 of the 2 patients who underwent localized R2 resections was given postoperative radiotherapy. This patient had no recurrence 4 years postoperatively. The other patient has had no postoperative problems, either. Patients with multicentric forms of the disease had different interventions: the 1 who had mixed-type CD and received postoperative chemotherapy was followed for 1 year postoperatively with no problems. The patient with plasma cellular CD first started corticosteroid treatment; however, since the lesion did not shrink, the patient was scheduled for chemotherapy at postoperative month 6.

Clinically, the potential for malignancy of local forms is rare and 5-year life expectancy was reported to be 100%. Long term follow-up is not recommended. However, long-term follow-up is recommended for patients with multicentric CD due to their increased risk for developing multiple myeloma, B cell lymphoma, Hodgkin lymphoma, or Kaposi sarcoma. Median survival rate of patients with multicentric CD is 29 months; mortality was reported as 26% within 1 year of diagnosis (4,6,8,10). Two patients with multicentric-type CD in the present study were followed during the first year and the sixth month, respectively, without any problems.

In conclusion, CD is a rare lymphoproliferative disease that can affect every part of the thorax, most commonly the mediastinum and hilum. Preoperative diagnosis is difficult, and lesions can serve as a great mimic. Surgical excision is an acceptable approach, both for diagnosis and treatment. Aggressive forms with a multicentric manifestation may occur with plasma cellular CD but are uncommon with hyaline vascular CD. Complete excision is curative in the local form of CD. However, due to local invasion and hypervascularization, complete excision might not always be achieved. Multimodal treatment including chemotherapy is used for patients with the multicentric form of the disease and close follow-up of patients is recommended.

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