CASE REPORT

Unicentric mixed variant Castleman disease associated with Hashimoto disease: the role of PET/CT in staging and evaluating response to the treatment

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Abstract

Castleman disease (CD) is a rare atypical lymphoproliferative disease, pathologically classified as hyaline vascular, plasma cell type and mixed type variant. The underlying cause of CD is unknown, however, several theories including autoimmunity have been proposed. We describe a patient diagnosed with unicentric mixed variant CD and Hashimoto thyroiditis, concurrently. She was staged with fluorodeoxyglucose (FDG)-positron emission tomography (PET)/computed tomography (CT) and the disease was localized to the mediastinum. After 6 cycles of chemotherapy consisting of vincristine and prednisone, the mediastinal lymph nodes regressed, but did not disappear from the CT scan. However, FDG-PET/CT showed complete metabolic response. Although the role of FDG-PET/CT in staging and evaluation of treatment response is controversial, this case shows that PET/CT can be effective and even better for staging and response evaluation. This case is also unique as there is no case of CD in association with Hashimoto thyroiditis has been reported previously. However, the possibility of a coincidental association must be raised, especially when the high prevalence of Hashimoto thyroiditis is considered.

Keywords: Castleman disease; FDG-PET; Hashimoto thyroiditis.

Introduction

Castleman disease (CD) is a rare lymphoproliferative disease, which is histopathologically classified into hyaline vascular type, plasma cell type and mixed type [1]. Clinically, it is classified as unicentric or multicentric types.

Although the cause of this disorder has not been definitely established, chronic low-grade inflammation, immunodeficiency state and autoimmunity are the proposed pathogenetic mechanisms [2]. Several autoimmune diseases have been associated with CD, but no association with Hashimoto thyroiditis has been defined.

The standard for staging of the disease is contrast-enhanced computed tomography (CT). There is insufficient data in the literature about the role of [18F]fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT in staging and evaluating response to treatment. This case report discusses a patient with unicentric mixed type CD associated with Hashimoto thyroiditis, for whom staging and evaluation of response to therapy was done with FDG-PET/CT.

Case report

A 62-year-old woman was admitted to the hospital with atypical chest pain. The physical examination and electrocardiography were normal. Enlargement of the mediastinum was detected in the chest radiograph. The CT scan of the chest revealed multiple mediastinal
lymphadenopathies (LAPs) extending from the thyroid level to the aortic root and surrounding the major vascular structures. The largest lymph node diameter was 1.5 cm. An FDG-PET/CT scan was obtained to characterize the LAPs metabolically. The PET/CT study showed the presence of increased FDG uptake in the perivascular structures of the anterior mediastinum (Fig. 1A–C). The maximum standardized uptake value (SUV_{max}) for the mediastinal LAPs was 6.4. Also, a diffuse FDG uptake was determined in both lobes of the thyroid gland. As a result, the patient was suspected to have Hashimoto thyroiditis.

The patient underwent mediastinoscopy and biopsies from several mediastinal lymph nodes were performed. Histological analysis revealed hyaline vascular type CD in one lymph node and plasma cell type CD in 3 lymph nodes. Figure 1 FDG-PET/CT images at diagnosis: (A) selected coronal PET slice, (B) corresponding CT slice, (C) maximum intensity projection (MIP) image of PET data. FDG-PET/CT images after treatment: (D) coronal PET slice, (E) corresponding CT slice, (F) MIP image of PET data.
nodes. So, the final diagnosis was mixed type CD (Fig. 2).

Laboratory evaluation showed anaemia of chronic disease (Hb 9.3 g/dl), elevated erythrocyte sedimentation rate (65 mm/h), mild elevation of serum IgG level (17.1 g/l, normal limits 7–15 g/l), and hypothyroidism (thyroid stimulating hormone 24.98 μIU/ml). There was no monoclonal peak in serum and urine immune electrophoresis. The patient was negative for human immunodeficiency virus. Bone marrow aspiration and biopsy showed a normocellular bone marrow with no increase in plasma cell count.

Thyroid ultrasonography revealed a nodular pattern consistent with Hashimoto thyroiditis. Fine-needle aspiration biopsy of the thyroid gland was performed. Antithyroglobulin antibody level was >4000 IU/ml (normal range 0–115 IU/ml) and her antithyroid peroxidase antibody level was 331.7 IU/ml (normal range 0–34 IU/ml). The patient was diagnosed as Hashimoto thyroiditis and levothyroxine 0.1 mg was initiated. Further evaluation for autoimmune diseases showed no disorders other than Hashimoto thyroiditis.

Due to the close relationship of the LAPs to the major vascular structures, complete surgical resection was not feasible. As the patient had a medical history of asthma and mild cardiac dysfunction, mediastinal radiotherapy was not considered to avoid cardiac and pulmonary toxicity. The patient received 8 cycles of vincristine (2 mg, day 1) and prednisolone (100 mg, days 1–5), every 2 weeks. After 8 cycles of chemotherapy, the LAPs had regressed 30% in diameter on chest CT. The PET/CT showed complete metabolic response (Fig. 1D–F). During the 42-month follow-up, no clinical and radiological signs suggestive of recurrence have been seen.

**Discussion**

CD is a polyclonal lymphoproliferative disease, characterized by lymph node enlargement with distinctive histological and clinical features. It has been divided clinically into unicentric and multicentric types, and histopathologically into hyaline vascular type, plasma cell type and mixed type[2] The hyaline vascular variant is the most common, comprising 90% of cases and is characterized by a benign clinical course[1,2]. In contrast, the plasma cell variant accounts for 9% of cases and tends to be clinically aggressive[1,2]. The mixed variant accounts for only 1% of cases. The hyaline vascular variant is...
generally unicentric and presents with mediastinal disease \cite{21}. Malignant transformation and systemic findings such as fever and anaemia are rare in this variant of CD. The plasma cell variant is generally multicentric and in contrast to the hyaline vascular type, systemic findings are frequently encountered, as well as a high risk of malignant transformation \cite{11}. Mixed variant CD is mostly multicentric, however, as in our patient, some patients with unicentric CD reveal features of both hyaline vascular type and plasma cell type \cite{31}.

Although the cause of CD is unknown; chronic low-grade inflammation, immunodeficiency state and autoimmunity have been proposed as likely pathogenic mechanisms \cite{1,2,21}. Numerous autoimmune diseases are associated with CD including Sjögren syndrome and rheumatoid arthritis \cite{21}. Dysregulated interleukin-6 production may play a key role in the pathogenesis of CD \cite{44}. In our case, the patient was diagnosed as CD and Hashimoto thyroiditis at the same time. There is no other case of CD accompanied by Hashimoto thyroiditis in the literature. It is not clear if autoimmunity is the underlying cause of CD, as it has been suggested that CD can alter the immune system and might lead to development of such an autoimmune disease \cite{35}. So, the autoimmune diseases can be the cause or the result of CD. Although they may share a common pathogenic pathway related to immune dysregulation, the possibility of a coincidental association must also be raised, especially when the high prevalence of Hashimoto thyroiditis is considered.

The standard modality for the evaluation of disease extent is contrast-enhanced CT, which shows enhancement due to hypervascularity of the lesions. Although the value of FDG-PET/CT in staging has been reported in a few cases, currently the role of FDG-PET/CT in diagnosis and in staging is still controversial \cite{6,10,18,21}. In a case presented by Pelosi et al. \cite{21}, it was stated that PET/CT could be considered in staging or restaging the disease and evaluation of response to the treatment. In our case, FDG-PET/CT correctly staged CD at diagnosis and was superior to CT scan in response evaluation. Although CT evaluation demonstrated a partial radiological response, the PET/CT revealed complete metabolic response. Thus, FDG-PET/CT seems to be useful for both assessment of the extent of the disease and response evaluation.

The treatment of CD depends on the extent and in some circumstances on the histological subtype \cite{1,2,21}. Complete surgical resection is the standard of care in unicentric CD. The 5-year survival rate after complete resection is approximately 100% \cite{22}. Radiotherapy is the best choice if complete resection is not possible; especially for the plasma cell variant. The 5-year survival rate after radiotherapy is 75%. In contrast to the unicentric variant, the multicentric variant necessitates aggressive systemic therapy due to its high malignant transformation potential and poor prognosis \cite{22}. The systemic treatment options are immunosuppression, cytoreductive agents, immunomodulators (steroids, interferon-alpha, thalidomide) and monoclonal antibodies (anti-interleukin 6, rituximab) \cite{1,2,12}. In this case, we achieved a durable complete response with chemotherapy in the absence of local therapy such as surgery or radiotherapy.

### Conclusion

This case report shows that FDG-PET/CT can have an important role in the staging and evaluation of treatment response in CD. We suggest that due to the rapid progression and high metabolic activity of the mixed type variant and the plasma cell variant, assessment of treatment response can be done with PET-CT. This case is also unique as there no case of CD in association with Hashimoto thyroiditis has been reported previously.

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