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IgG4-related disease simulating Hodgkin lymphoma in a child

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Abstract Immunoglobulin (Ig) G4-related disease is a recently described syndrome characterized by mass forming lymphoplasmacytic tissue infiltration and elevated serum IgG4 concentrations usually affecting middle-aged or older individuals. Lymphadenopathy is frequently observed and is sometimes the first or only manifestation of the disease. We report a case of IgG4-related disease mimicking Hodgkin lymphoma in a 13-year-old girl. The patient presented with progressive unilateral cervical lymphadenopathy of several months duration. Biopsy showed follicular hyperplasia with progressive transformation of germinal centers. Interfollicular areas were expanded by small lymphocytes, histiocytes, eosinophils and fibrosis with occasional CD30 positive cells initially concerning for interfollicular Hodgkin lymphoma. Immunohistochemical analysis revealed an intrafollicular plasmacytosis with an IgG4-positive/IgG-positive plasma cell ratio of 50% supporting a diagnosis of IgG4-related lymphadenopathy, progressively transformed germinal centers type. Laboratory studies were supportive with elevated serum IgG4 (178 mg/dL) and IgE (30.40 kU/L) levels along with an elevated serum IgG4/IgG ratio (0.16). Very few cases of IgG4-related disease have been described in children. Within this age group, there is considerable clinical overlap between IgG4-related disease associated lymphadenopathy and Hodgkin lymphoma. In addition, lymphadenopathy secondary to IgG4-related disease demonstrates substantial histologic diversity with the potential to simulate the inflammatory background and fibrosis of Hodgkin lymphoma. The importance of accurate diagnosis is underscored by the prognostic implications considering the marked response of the syndrome to steroid therapy. In addition, appropriate follow up is critical to monitor for relapse and additional organ involvement.

1. Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a recently described syndrome characterized by lymphoplasmacytic tissue infiltration rich in IgG4-positive plasma cells and elevated serum IgG4 concentrations usually affecting middle-aged or older individuals [1]. It was originally described in the setting of autoimmune pancreatitis but has subsequently been reported in practically every organ [2–4]. Lymphadenopathy is observed in up to 80% of patients, and is sometimes the presenting manifestation of the disease [5,6]. There is usually a marked and sustained response of IgG4-RD to steroid therapy although some cases may recur or progress to involve multiple organ systems [1,4]. Diagnosis of IgG4-related lymphadenopathy is complicated by diverse histologic patterns of lymph node involvement

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including multicentric Castleman disease-like pattern, follicular hyperplasia, interfollicular expansion, progressive transformation of germinal centers (PTGC), and nodal inflammatory pseudotumor-like pattern [7–10]. We describe a pediatric patient with lymphadenopathy due to IgG4-related disease with a clinicopathologic picture mimicking Hodgkin lymphoma. Few cases of IgG4-RD have been reported in children; pancreatic, orbital and sinonasal involvement have been documented in addition to a recent report of an infant with pulmonary disease, a mediastinal mass and lymphadenopathies. To our knowledge, this is the first reported case of IgG4-RD presenting as palpable lymphadenopathy in the pediatric population [11–14].

2. Case report

A 13 year old girl presented with a three month history of an enlarging right neck mass. She reported fatigue but denied fevers, night sweats and weight loss. Pharmacologic therapy with three courses of antibiotics did not lead to improvement. CT scanning revealed right cervical lymphadenopathy with enlarged lymph nodes up to 3.3 cm. Laboratory evaluation was unremarkable except for an elevated erythrocyte sedimentation rate (40 mm/h). Serology studies for Epstein Bar virus and cytomegalovirus were negative.

The patient was referred for open biopsy given the clinical concern for lymphoma. Biopsy of the largest node demonstrated follicular hyperplasia and PTGC. The interfollicular areas were expanded by small lymphocytes, histiocytes and eosinophils with focal areas of fibrosis. Scattered large CD30+ cells were present, however, no definite Reed–Sternberg cells were identified. Flow cytometry revealed polytypic B-cells and unremarkable T-cells with only a 1% population of dual positive CD4 and CD8 T-cells. Plasma cells were not studied. The findings were initially worrisome for an early interfollicular Hodgkin lymphoma and close clinical follow-up was recommended. An 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) scan revealed a 2 cm mass posterior to the right parotid gland as well as numerous bilateral FDG avid enlarged cervical lymph nodes and an area of uptake within the right nasopharynx, highly suspicious for malignancy (Fig. 1).

The patient proceeded to excision of the right neck mass along with lymph node and nasopharyngeal biopsies. Histologic examination of the neck mass and lymph nodes demonstrated findings similar to the original biopsy (Fig. 2). The nasopharyngeal biopsies revealed respiratory mucosa with underlying lymphoid tissue with similar findings including follicular hyperplasia and PTGC. Further evaluation revealed a prominent intrafollicular plasmacytosis with rare interfollicular plasma cells. Immunohistochemical staining performed on the lymph node biopsies and neck mass revealed a large number of intrafollicular IgG4 positive plasma cells with an

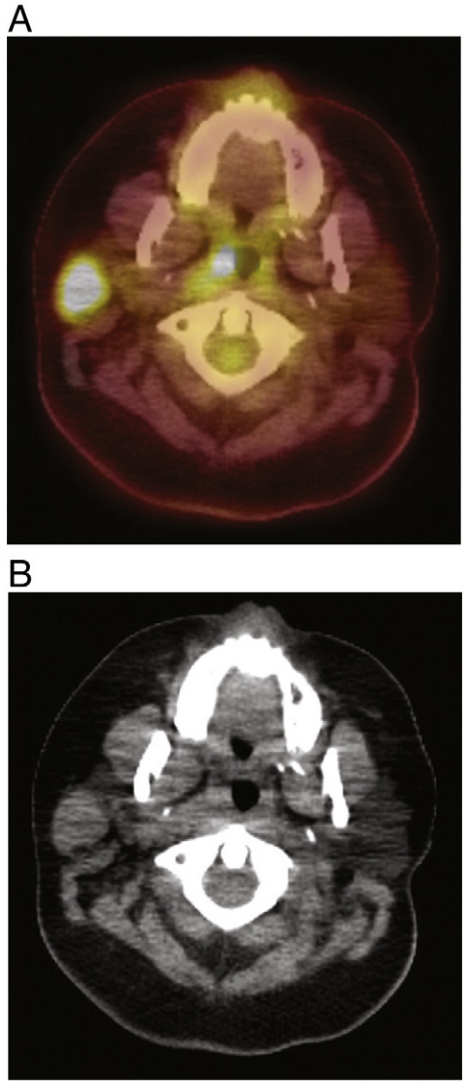

Fig. 1 Positron emission tomography/computed tomography of the neck (PET/CT). A, There is a right neck mass posterior to the right parotid and bilateral cervical adenopathy. B, There is avid FDG uptake in the right neck mass and focally in the right nasopharynx on PET/CT scan.

IgG4+/IgG+ plasma cell ratio of greater than 40% and areas with more than 100 IgG4-positive cells per high powered field supportive of IgG4-related disease. Subsequent serum studies were performed demonstrating elevated IgG-4 (178 mg/dL) and IgE (30.4 kU/L) levels. The patient was diagnosed with IgG4-related disease associated lymphadenopathy, progressive transformation of germinal centers type.

3. Discussion

IgG4-related disease is a lymphoproliferative disorder characterized by elevated serum IgG4 concentrations and mass forming tissue infiltration by IgG4 positive plasma cells and lymphocytes often accompanied by fibrotic