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 plasma cytosis 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.

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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.
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 polyclonal 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 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
changes in the affected organ [15]. There is a diverse range of clinical presentations ranging from single organ involvement or lymphadenopathy to complex presentations with lesions in multiple organs synchronously [3,5]. Constitutional symptoms such as fever and weight loss are usually absent [4,15]. The diagnosis of IgG4-RD is based upon unique histologic features including infiltration by IgG4-positive polyclonal plasma cells with a IgG4/IgG positive plasma cell ratio of greater than 40% and more than 40 IgG4+ plasma cells per high power field, although this may vary by site and comprehensive diagnostic criteria must be fulfilled [15,16]. Serum IgG4 levels greater than 135 mg/dL support the diagnosis [16,17]. Additional laboratory findings suggestive of IgG4-RD include polyclonal hypergammaglobulinemia, hypocomplementemia, increased serum IgE concentrations and elevated erythrocyte sedimentation rate [6,7]. Radiologically, IgG4-RD is characteristically FDG avid on PET/CT which can be misinterpreted as malignancy, especially in the setting of multifocal disease [18]. Patients generally show a marked response to corticosteroid therapy, however, the disease course may vary from complete resolution to multiple recurrences with additional organ involvement. In addition, several studies have demonstrated a possible increased risk of subsequent malignancy. Long term clinical follow up is necessary [1,4].

To our knowledge, this is the first reported case of IgG4-RD presenting as palpable lymphadenopathy in a pediatric patient. Although there have been reported cases of IgG4-RD presenting as palpable lymphadenopathy in patients as young as 19 years in addition to lymphadenopathy in conjunction with systemic disease in a 22 month old infant, the majority of previous reports describe IgG4-RD associated lymphadenopathy to occur within the middle aged to elderly population [10,19]. It has been previously suggested that this may in part be due to a bias in clinical management as well as diagnostic evaluation. Benign and reactive lymphadenopathy is more common in younger patients but affected lymph nodes are less often excised [19]. In addition, differences in the subsequent diagnostic work-up may lead to pediatric cases going unrecognized.

Within the pediatric age group, there are unique considerations in the diagnostic approach to persistent lymphadenopathy. There is a relatively high prevalence of malignancy in lymph node biopsies at pediatric referral centers ranging from 13% to 27%; of these Hodgkin lymphoma is the most common diagnosis [20–22].
Histologically, there is overlap between some of the patterns of IgG4-RD associated lymphadenopathy and Hodgkin lymphoma. In the present case, the interfollicular expansion by lymphocytes, histiocytes and eosinophils with areas of fibrosis was concerning for the inflammatory cell milieu of Hodgkin lymphoma, and an interfollicular Hodgkin lymphoma was considered. While classic Reed–Sternberg cells were not identified, scattered immunoblasts were morphologically similar to Hodgkin Reed–Sternberg variant cells, uninucleate cells with irregular nuclei and large nucleoli. The progressive transformation of germinal centers pattern raises additional diagnostic considerations including typical PTGC and early nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) [23–25]. Typical PTGC, however, does not generally show interfollicular expansion, interfollicular plasma cells and eosinophils or areas of fibrosis more consistent with IgG4-RD [9].

In addition to overlapping morphologic features, flow cytometry demonstrated a subset of T-cells expressing both CD4 and CD8 (1%); a finding which may be present in NLPHL, although in more abundant numbers and generally a non-specific finding [26]. Coexpression of CD4 and CD8 has also been described in IgG4-related lymphadenopathy ranging from 1% to 6% of lymphocytes analyzed and was seen at a higher rate with concomitant progressively transformed germinal centers on histology [19].

In summary, we report a unique presentation of IgG4-RD associated lymphadenopathy in a child. Within this age group, the differential diagnosis with Hodgkin lymphoma is a prominent consideration. The importance of accurate diagnosis is underscored by the significant therapeutic and prognostic implications considering the marked response of the disease to steroid therapy. Pathologists should be aware of the variable histologic patterns of IgG4-RD, the possibility of a young age at presentation and its potential to simulate malignancy.

Disclosure/conflict of interest

The authors have no conflicts of interest to disclose.

References