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Multiple Organ Involvements in a Case of IgG4 Related Disease

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Abstract

A 64-year-old woman with presentation of proptosis referred to Rheumatologic clinic at Amir- Alam hospital. The result of physical exam revealed that there was a left eye proptosis with 29 mm in size and no light perception. Computed tomography showed mass infiltration to left carotid sheet and mandibular foramen. Besides, there was an increase in hepatic vascularity and peri-portal infiltration predominantly in the left lobe that caused intra-hepatic duct dilation. Despite of the deterioration of the proptosis and visual acuity, probably due to limited knowledge about IgG4-RD, the patient did not receive the appropriate treatment. Unfortunately, this issue caused significant reduction in the visual acuity (no light perception). Finally, pathology and IHC study revealed presence of CD20+ plasma cell up to 60% per High power field and with the diagnosis of IgG4-RD, methylprednisolone and cyclophosphamide initiated and we observed a significant reduction of symptoms.

Keywords: IgG4-related disease • IgG4-related orbitopathy • Proptosis • Visual acuity • Head and neck involvement • IgG4-related hepatopathy

Introduction

IgG4-RD has been recently proposed by a group of Japanese investigators to encompass a variety of clinical and pathological entities previously considered as a separate disease [1]. Now it is a newly recognized fibroinflammatory disease by multiple features including mass forming lesion; a dense lymphoplasmacytic infiltrate; a characteristic histopathological appearance and often elevated serum of IgG4. The disease was first recognized in pancreas that today is known as autoimmune pancreatitis type 1 [2]. The main pathologic features include dense lymphoplasmacytic infiltrates of small lymphocytes and plasma cells, fibrosis with storiform pattern and obliterative phlebitis. IgG4-RD can mimic malignant, infective and inflammatory disorders so it is important to differentiate this disease from the other mimickers and pathologic findings are the most helpers [3]. Main features of IgG4-RD include sialoadenitis, autoimmune pancreatitis, dacryoadenitis, lymphadenopathy, retroperitoneal fibrosis and sclerosing cholangitis. [2].

Case Presentation

A 64-year-old woman with presentation of left eye proptosis for 5 years and bilateral nasal polyps from 2 years ago referred to the Rheumatology clinic at Amir- Alam hospital. Physical examination revealed a left eye proptosis with 29 mm in size and no light perception (Figure 1).

Figure 1. This picture is shot before the initiation of the treatment. Notice the left eye proptosis.

The right eye was normal. She had a corneal scar due to a prolonged conjunctivitis. A mild periorbital edema was seen in her left eye. There were no lymphadenopathies, hepatosplenomegaly or malar rash. In June 2017, diagnostic FESS (Functional Endoscopic Sinus Surgery) was done and she was diagnosed with diffused Sino nasal polyposis. As the patient also had significant proptosis (29 mm), the polypectomy and orbital decompression was done. Computed tomography showed infiltrative left orbit mass with extraocular and peri-neural involvement with extension to orbital apex and diffuse subcutaneous infiltration of left side of scalp (Figure 2).

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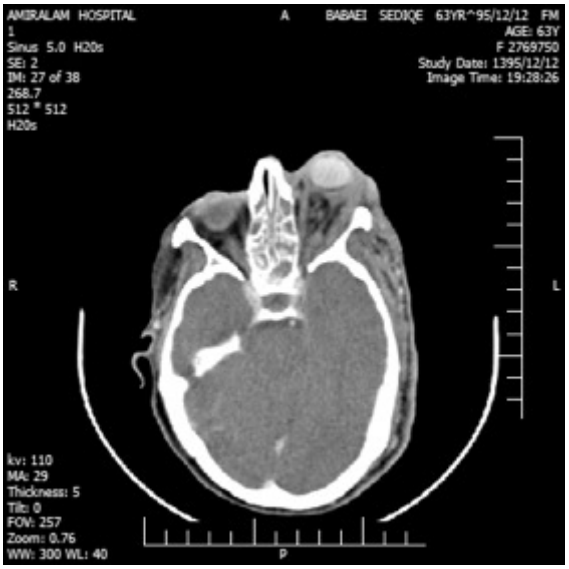

Figure 2. CT shows infiltrative left orbit mass with extraocular and perineural involvement with extension to orbital apex and diffuse subcutaneous infiltration of left side of scalp.

Multiple lymphadenopathy in the left side with maximum SAD (11 mm). Mass infiltration to left carotid sheet and mandibular foramen was notable. No lung and mediastinal lesion was detected. Abdomino pelvic computed tomography was done. There was an increase in hepatic vascularity and peri-portal infiltration predominantly in the left lobe that caused intra-hepatic duct dilation (Figure 3). Neither retroperitoneal fibrosis nor pancreatitis was detected.

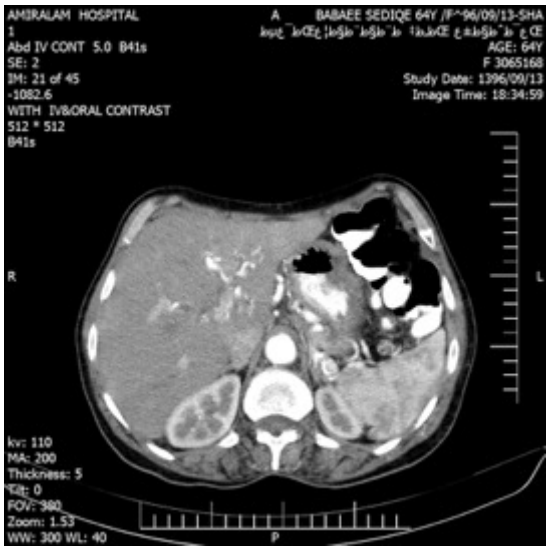

Figure 3. CT of the abdomen shows an increase in hepatic vascularity and peri-portal infiltration predominantly in the left lobe that cause intra- hepatic duct dilation.

In the microscopy finding of both nasal cavities content, unspecific chronic inflammatory process was seen however, pathology of the left orbital content showed lymphoid hyperplasia in association with plasmacytic and eosinophilic infiltrate which was suggestive for IgG4-RD. Immunohistochemical (IHC) staining revealed characteristic features of IgG4-RD with positive CD20 in germinal cell of follicle, positive CD3 in Para follicular cells, positive CD138 in plasma cells, IgG: positive in plasma cells. Up to 60 IgG4 positive plasma cells were seen per High power field (HPF) with IgG4/IgG more than 40%. Serum IgG4 level was 369 mg/dL more than 135 mg/dL.

On Echocardiography, the Ejection Fraction (EF) of LV was 55% with normal LV and RV size, mild mitral and tricuspid regurgitation, and normal Pulmonary Arterial Pressure (PAP). The urinalysis was normal. On systemic blood examination, she had an anemia (Hemoglobin: 10.3 and MCV: 77.6), she had an elevated ESR: 48, there was also slightly elevated ALP: 298 and the rest of the examinations were normal.

With the diagnosis of IgG4 related disease, treatment of methylprednisolone 1 gram/day for 3 consecutive days and 1 gr cyclophosphamide. Then the treatment was continued with 50 mg oral prednisolone (1 mg/kg) that was tapered to 5 mg daily within 3 months in addition to monthly pulse of cyclophosphamide. The patient responded dramatically to the treatment and scalp infilteration resolved the eye proptosis decreased significantly to 19 mm and as well as visual acuity changed to light perception.

During the follow up, we detected a rise in liver enzymes as a result, we substituted cyclophosphamide with Rituximab and we observed that the left carotid sheet infiltration and pre-ductal infiltration in liver were resolved.

Discussion

Many reports of IgG4 related disease have come from east Asia but this does not indicate necessarily that the disease is more prevalent in there than elsewhere. Awareness of the disease has been rise later in other parts of the world and this could be the cause of variation in reports.

The estimated incidence of 0.2 to 1/100 000 in Japan and no available incidence data in occidental countries was reported [4].

The annual incidence of IgG4-RD was estimated at 0.28–1.08/100,000. a prevalence of ~62 patients per million inhabitants were expected in Japan in 2009 [5].

IgG4-RD usually affects individuals of middle to upper age, with an onset at 50–70 years [6-8] although rare pediatric cases have been described, the youngest being 5 years old [9-12]. Most studies report an overall predilection for the male sex, [9-12] especially for IgG4-related pancreatitis with a M: F ratio of 2.8 to 7.5: 1 [13,14]. However, for IgG4-related ophthalmic disease the male to female ratio is almost equal and head and neck disease may occur more frequently among females [15].

The number of patients presenting with IgG4-ROD who have systematic involvement of the disease varies from 22% to 100% with an average of 50% from 5 studies [16-20].

In this case, the patient had come with the manifestation of proptosis and due to diagnostic delay as well as delay in the treatment, suffered from the complications of the IgG4-RD as decrease in visual acuity. The primary pathology from the patient`s optical mass reported chronic inflammatory pseudotumor and the patient had no other clinical complaints. Despite of the pathology report, expansion of the disease and deterioration of the proptosis and visual acuity, probably due to limited knowledge about the prevalence, manifestations and progression of the IgG4-RD in 6-7 years ago, the patient did not receive the appropriate treatment. Unfortunately, this issue caused significant reduction in the visual acuity (no light perception) Finally, in the last biopsy from the patient`s retro-orbital mass, the pathologic sample was evaluated for IgG4 staining and the ratio of IgG4/IgG as well as IgG4 level of the serum was evaluated too. The diagnosis of the IgG4-RD was established as the result of IHC revealed the presence of IgG4 positive plasma cells, the ratio of IgG4-RD >40% and serum IgG4 level > 130 mg/L (369 mg/L). Although, Sino-nasal polyps are common in IgG4-RD however, the microscopic findings of the patient's polyps in contrast to the pathology of orbits were not specific. Early aggressive treatment (pulse of cyclophosphamide and pulse of corticosteroids) started hoping to save the vision of the patient but unfortunately due to severity of injury to the optic nerve, there was no improvement in the visual acuity of the patient. The author previously reported a similar case of IgG4-RD with skin involvement

[21] and relate the scalp involvement in this case to the IgG4-RD since it was resolved with the treatment in any patients with organ-threatening or refractory disease or whom treatment with immunomodulatory drugs was unsuccessful, treatment with rituximab is recommended [22]. As in this case with the treatment of Rituximab, left carotid sheet infiltration and peri-ductal infiltration in liver were resolved.

Head and neck involvement is one of the most common presentations of IgG4-RD [23]. It can represent itself with dacro-cystitis, sialadenitis, inflammatory pseudotumor, orbital myositis as well as sinusitis and IgG4-related thyroid disease [24]. In our patient Computed tomography showed infiltrative left orbit mass with extraocular and peri-neural involvement with extension to orbital apex and diffuse subcutaneous infiltration of left side of scalp. Multiple lymphadenopathies in the left side with maximum SAD (11 mm). Mass infiltration to left carotid sheet and mandibular foramen was notable that shows diferent features of IgG4-RD in multiple organ involvement.

Histopathology is still the gold standard for the diagnosis of IgG4-RD and also to distinguish between benign and malignant lesions, because it can mimic neoplastic infiltration pattern. Thus, for the diagnosis of IgG4-RD, we should exclude other diseases such as granulomatous with polyangiitis [GPA], Sarcoidosis, Sjogren, orbital cellulitis, thyroid orbitopathy and malignant causes including lymphomas [25].

IgG4-sclerosing cholangitis is the biliary manifestation of IgG4-RD [26], and is the most common extra pancreatic manifestation of Autoimmune pancreatitis (AIP) type 1 [27]. IgG4-SC affects usually males at 50-60 years of age. It is usually presented as obstructive jaundice, weight loss and abdominal pain, with jaundice being the most common finding in 70-80% of patients [28].

IgG4-sclerosing cholangitis is a common presentation of IgG4-RD which needs a complete approach to establish the diagnosis. It is important to differentiate IgG4-sclerosing cholangitis from other benign and malignant causes [27].

Currently treatment regimens of biliary and hepatic involvement in IgG4-RD remains ill defined, but still steroid therapy and evaluation of the response is the first line unless contraindicated [27].

In this case, during the hospitalization, we evaluate the patient for other organ involvements. In the contrast CT scan, peri-portal infiltrations led to increased hepatic density and IHC dilation in some hepatic areas. As for the hepatic involvement in IgG4-RD that can present as inflammatory pseudotumor with or without sclerosing cholangitis in hepatobiliary system, and also rise in the ALP [28] of the patient, we related these hepatic findings to the IgG4-RD. However, as a limitation in our work, the patient refused to perform liver biopsy. The appearance of the pancreas was normal but according to the infiltrations of carotid sheath and great cervical vessels, aggressive treatment started for the patient.

IgG4-RD is a benign disease that responds very well to the treatment with corticosteroids but discontinuation of the treatment may cause a relapse of the disease. The clinical manifestations of the IgG4-RD depend on the disease activity and expansions to other organs. IgG4-sclerosing cholangitis (IgG4-SC) often is presented as obstructive jaundice (70-80%) associated with abdominal pain and loss in weight [29]. Also, IgG4-Hepatobilliary disease (IgG4-HBD) may be asymptomatic and get detected accidentally during cross sectional imaging for other reasons [30]. Often, liver function tests in IgG4-HBD are abnormal. Rise in bilirubin, ALP and GGT, are the most common seen abnormalities and in IgG4-SC elevation in transaminase is more frequent [29].

Two types have been described histologically, lymphoplasmacytic and fibrohistocytic but only the former has the characteristic features of the disease. IgG4-HBD shows five histologic pattern including portal inflammation, large bile duct obstructions, portal sclerosis, lobular hepatitis and canalicular cholestasis [29,30].

Conclusion

In any patient with chronic tumor like lesions and pseudotumors without evidence of malignancy, we should think of IgG4 related disease. In this circumstance, biopsy may lead us to the definitive diagnosis. From this case, we learn that we should treat the patients with IgG4-RD in time, in order to avoid irreversible organ dysfunction.

Ethical Approval

All procedures performed in study involving human participant were in accordance with the ethical standards of the institutional research committee and with the ethical standards.

Informed Consent

Informed consent was obtained from the patient participated in the study. Written permission from the patient was taken for publication of this work with her photo.

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Conflict of Interest

None of the authors have any conflict of interest.

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