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Adult Onset Asthma and Periocular Xanthogranuloma (AAPOX), a Rare Entity With a Strong Link to IgG4-Related Disease

An Observational Case Report Study

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Abstract: Adult onset asthma and periocular xanthogranuloma (AAPOX) is a rare non-Langerhans histiocytosis characterized histopathologically by a periocular infiltration of foamy histiocytes and Touton giant cells. Benign hyperplasia with plasma cell infiltration is classically described in eyelids or lymph nodes of AAPOX patients. It is also a characteristic feature of IgG4-related disease (IgG4-RD), a new entity defined by an IgG4-bearing plasma cell infiltration of organs.

To determine if AAPOX syndrome shares clinical, biological, and histopathological characteristics with IgG4-RD, we used the comprehensive clinical diagnostic criteria for IgG4-RD in a retrospective case series of three consecutive patients with histologically-proven AAPOX. Patients who were diagnosed with AAPOX at a French academic referral center for orbital inflammation between November 1996 and March 2013 were enrolled. Biopsies from ocular adnexa or other organs were systematically reexamined. For each patient, clinical and serological data, radiologic findings, and treatment were retrospectively analyzed.

Two AAPOX patients fulfilled all of the diagnostic criteria for a definite IgG4-RD. One patient who lacked the serological criteria fulfilled the criteria of a probable IgG4-RD.

These 3 cases of AAPOX patients fulfilled the IgG4-RD comprehensive clinical diagnostic criteria. To our knowledge, this is the first observational case report study to clearly show a strong relationship between IgG4-RD and AAPOX syndrome.

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Abbreviations: AAPOX = adult onset asthma and periocular xanthogranuloma, CD = cluster of differentiation, FDG PET/CT = fluorodeoxyglucose-positron emission tomography/computerized tomography, IgG4-RD = IgG4-related disease, MRI = magnetic resonance imaging.

INTRODUCTION

Adult onset asthma with periorbital granuloma (AAPOX) syndrome was first described in 1993 by Jakobiec et al and is considered to be a periorbital disease with a specific granulomatous inflammation.[1,2] Palpebral biopsy shows multinucleated histiocytes with a foamy cytoplasm, referred to as Touton giant cells.[3] In a recent case series, we reported that palpebral biopsies from AAPOX patients showed large sheets of histiocytes between reactive lymphoid follicles.[4] Remarkably, we found polyclonal plasma cells within fibrous septa which is also seen in organs involved by IgG4-related disease (IgG4-RD).

IgG4-RD is a recently recognized entity with specific histological features and frequently with elevated serum IgG4 level.[5] The main histopathological characteristics of this systemic disease are an association of lymphoplasmacytic infiltrate with increased number of IgG4-positive plasma cells, storiform-type fibrosis, and obliterative phlebitis. Specific histopathological findings vary depending on the different organs involved.[6]

Based on our previous histological findings, we hypothesized that patients with AAPOX could satisfy the comprehensive clinical diagnostic criteria for IgG4-RD. In the present study, we verified that three consecutive patients with AAPOX syndrome met such criteria.

MATERIALS AND METHODS

The patients were recruited in a French academic referral center for orbital inflammation where they were managed for a xanthogranulomatous disease. AAPOX syndrome was diagnosed on the basis of the criteria defined by Jakobiec et al[1]; an adult onset asthma associated with a periorbital xanthogranuloma. Three consecutive patients with biopsy-proven AAPOX were enrolled between November 1996 and March 2013. Two of them (Cases 1 and 2) have been previously described in a published case series.[4] In our previous report,

foamy histiocytes were found in Patient 2 only by retrospective analysis of the eyelid biopsy. However, no Touton cells were identified as they were for Patient 1.[4] For this reason, we herein used for Patient 2 additional eyelid biopsy specimens that were reviewed to provide evidence of Touton giant cells.

For the purpose of this study, these 3 patients with histologically proven AAPOX syndrome were reviewed retrospectively. In addition to ocular adnexal biopsy, a salivary glands or a cheek biopsy was performed in all AAPOX patients. Histopathological findings were reexamined by hematoxylin and eosin staining and by additional immunohistochemical staining using anti-CD3 antibody (rabbit polyclonal anti-human CD3; DakoCytomation, Glostrup, Denmark), anti-CD20 antibody (mouse monoclonal anti-human CD20 clone L26; Ventana-Roche, Tuscon, USA), anti-CD38 antibody (mouse monoclonal anti-human CD138 clone BA38, Ventana-Roche), anti-IgG antibody (rabbit polyclonal anti-IgG antibody, Ventana-Roche), and anti-IgG4 antibody (rabbit monoclonal anti-human IgG4 antibody clone EP4420, GeneTex, Irvine, USA). To count IgG4-plasma cells, we used 3 X40 fields with the highest number of IgG4 + plasma cells and calculated the average number of IgG4 + plasma cells within these fields.[7(p4)]

As positive control, we used a biopsy specimen of orbital lesion and minor salivary glands from a patient with definite IgG4-RD we previously reported.[8] As negative control, an orbital biopsy from a patient with nonspecific orbital inflammation and a biopsy specimen of minor salivary glands from a patient with genuine Sjögren syndrome with marked lymphocytic infiltration were also reviewed and additional IgG4 immunostaining were realized.

The morphologic data from orbital MRI and/or FDG PET/CT, laboratory data including serum IgG4 and IgE levels at presentation and the clinical response to treatment were recorded.

The diagnosis of IgG4-RD was defined using the 2012 comprehensive clinical diagnostic criteria for IgG4-RD.[9] Tissue specimens with more than 10 IgG4-positive plasma cells per high-power field and with a ratio of IgG4+/IgG + plasma cells of more than 40% were considered positive. Elevated serum IgG4 concentration was defined by a concentration higher than 1.35 mg/L. Differential diagnosis of IgG4-RD such as sarcoidosis, Castleman's disease, granulomatosis with polyangeitis (Wegener disease), lymphoma, and cancer were excluded. IgG4-RD was considered definite when patients fulfilled all the criteria and probable when only the elevated serum IgG4 concentrations were not present.

The ethics committee (Comité de protection des personnes CPP Ile-de-France III, D. Simhon) was consulted and as per their response, in our country, this retrospective study did not need an ethical approval and thereby, did not involve written informed consent.

RESULTS

We describe 3 patients with AAPOX. Cases 1 and 2 have been previously described in a published case series.[4] Two AAPOX patients (Cases 2 and 3) had the characteristic features of a definite IgG4-RD. One case (the first patient) had the characteristic features of a probable IgG4-RD (Tables 1 and 2).

Case 1

A 65-year-old white male presented with a 10-year history of bilateral yellow swelling of the upper and lower eyelids (Fig. 1, A1). Surgical reduction was attempted twice at 5-year intervals, but was always followed by relapse. Cervical adenopathy and a soft tissue mass of the left cheek were found on examination. The patient reported having sinusitis and adult onset asthma that started 3 years before the periocular infiltration. He had a history of elevated IgE.

At presentation, laboratory tests were normal except for an eosinophil blood cell count of 920/mm^3 and for polyclonal hypergammaglobulinemia with a total IgG level of 17 g/L. Immunophenotyping of blood lymphocytes and T cell clonality did not reveal any sign of lymphoproliferative syndrome. Serum IgG4 level, assessed retrospectively, was 1 g/L. An orbital MRI confirmed bilateral preseptal and anterior orbital infiltration, and lacrimal gland hypertrophy (Fig. 1, A2). The palpebral biopsy revealed fibrous septa infiltrated by numerous foamy histiocytes, characteristic Touton giant cells as well as IgG4 + plasma cells after immunostaining (Fig. 2, A1 and B1). A subcutaneous tissue biopsy of the left cheek showed both xanthogranulomatous reaction with Touton giant cells and benign lymphoid hyperplasia organized in follicular germinal centers (Fig. 3, A1). B- and T-cell clonality on the left cheek tissue sample was negative by polymerase chain reaction analysis for clonal rearrangement of the T-cell receptor gamma chain gene or clonal immunoglobulin rearrangement. Reexamination of the cheek biopsy demonstrated a significant IgG4 + plasma cell infiltrate (Fig. 3, B1). Oral prednisone, initiated at 1 mg/kg daily, led to a dramatic decrease of the eyelid swelling and of the size of the soft tissue mass in the left cheek. Asthma resolved after the patient started the corticosteroid treatment. Corticosteroids were then tapered to 5 mg daily without any relapse of ocular or systemic manifestations after 72 months of follow-up.

Case 2

A 52-year-old white male was referred for bilateral xanthomatous lesions of the eyelids (Fig. 1, B1). He had painless periorbital swelling increasing for 18 months. Four years before presentation, he developed late onset asthma for which he was taking inhaled corticosteroids and bronchodilators. He also had a history of mild obstructive sleep apnea syndrome and of disabling nasal obstruction. On clinical examination there was right inguinal lymphadenopathy. Laboratory tests were normal except for an eosinophil blood cell count of 730/mm^3, a serum IgE level of 292 UI/L (N < 100 IU/mL), an elevated gammaglobulin level with a serum total IgG level of 20.9 g/L. Serum IgG4 level assessed retrospectively, was 6.5 g/L. An orbital MRI revealed major bilateral hypertrophy and gadolinium contrast enhancement of the lacrimal glands and eyelids, with moderate right lateral rectus hypertrophy (Fig. 1, B2). On FDG PET/CT evaluation, the mediastinal and inguinal lymphadenopathies, the perirectal fat infiltration and the lacrimal glands and eyelids tumefaction were all hypermetabolic. An ocular adnexal biopsy, including palpebral tissue and lacrimal gland, showed follicular lymphoid hyperplasia with typical germinal centers among a population of foamy histiocytes. The reactive germinal centers of the follicles were clearly BCL2 negative. Reexamination of the entire biopsy specimen and of an additional tissue block enabled us to identify typical Touton giant cells which had not been described in a prior report (Fig. 2, A2).[4] The plasma cells admixed with the histiocytes stained IgG4 positive when stained with specific antibodies (Fig. 2, B2). A significant IgG4 + plasma cell infiltrate was also seen on an accessory salivary glands (Fig. 3, B2) and inguinal lymph node biopsies (data not shown). Oral prednisone initiated at 1 mg/kg daily and tapered to 5 mg daily led to a remarkable improvement of the

TABLE 1. Characteristics of Patients With AAPOX

	Patient 1	Patient 2	Patient 3
Age at onset/age at diagnosis (years)	55/65	48/52	24/33
Clinical features			
Ophthalmic presentation	Yellow-orange upper and lower eyelid mass Eyelid elevation compromised	Periocular swelling, orange colored Moderate exophthalmia	Left yellow-orange upper eyelid mass Periocular swelling
General presentation	Adult onset asthma Allergic sinusitis Cervical adenopathy Left cheek swelling	Late onset-asthma Moderate sleep obstructive apnea syndrome Allergic sinusitis Right inguinal adenopathy	Adult onset asthma Allergic sinusitis Bilateral axillary adenopathy
Laboratory findings			
Eo ($N < 500/mm^3$)	920	730	638
ANA	—	—	—
A-SSA	—	—	—
A-SSB	—	—	—
IgG4 ($N < 1.35$ g/L)	1	6.5	9.2
IgE ($N < 100$ UI/ml)	NA	292	1260
Radiologic findings			
MRI	Bilateral preseptal and anterior orbital infiltration Lacrimal gland hypertrophy	Bilateral hypertrophy of the lacrimal glands and eyelids, with moderate right lateral rectus hypertrophy	Bilateral hypertrophy of the lacrimal glands and eyelids
PET/CT	NA	Hypermetabolic lacrimal glands and eyelids Hypermetabolic mediastinal and inguinal enlarged lymph nodes Hypermetabolic fat infiltration in presternal, mesorectal and peri-pyelic locations	Hypermetabolic hypertrophy of the lacrimal glands Hypermetabolic mediastinal and axillary enlarged lymph nodes

ANA = antinuclear antibody, A-SSA = anti-SSA antibody, A-SSB = anti-SSB antibody, Eo = eosinophil granulocytes, FDG = fluorodesoxyglu-fluorodesoxyglucose, MRI = magnetic resonance imaging, NA = not available, PET/CT = positron emission tomography-computed tomography.

palpebral swelling and systemic manifestations. Control serum electrophoresis and immunofixation were normal without the previously reported hypergammaglobulinemia. Low dose methotrexate was recently added when systemic manifestations relapsed, and after a follow-up of 72 months, the patient is doing well without any sign of relapse.

Case 3

A 33-year-old woman from North Africa was referred for a relapsing periocular xanthogranuloma (Fig. 1, A3). Nine years before, she had been successfully treated by prednisone initiated at a dose of 1 mg/kg daily. But, every time corticosteroids were tapered to 10 mg daily, orbital relapse occurred. She had an onset of asthma four years before presentation. She did not have history of recurrent upper or lower respiratory tract infections or of cutaneous infections. At presentation, laboratory tests revealed a normal blood count except for an eosinophil level of $638/mm^3$. Serum protein electrophoresis revealed an elevated gamma-globulin level with 14 g/L of total IgG. Serum IgG4 level was 9.2 g/L and IgE was elevated at 1260 IU/mL ($N < 100$ IU/mL).

MRI showed an enlargement of the lacrimal glands (Fig. 1, B3). PET/CT revealed FDG uptake of the lacrimal gland tumefaction and of axillary adenopathy. Reexamination of the ocular adnexal biopsy showed the presence of Touton giant cells admixed with IgG4 + plasma cells in the palpebral area (Fig. 2, A3 and B3). Reexamination of the salivary gland biopsy demonstrated the presence of follicular germinal centers mixed with plasma cells, predominantly of IgG4 isotype (Fig. 3, A3 and B3). Prednisone initiated at 1 mg/kg daily resulted in a dramatic decrease of the palpebral swelling and asthma. The patient relapsed when the corticosteroids were tapered to 10 mg daily. Low dose methotrexate was introduced as a corticosteroid sparing agent and corticosteroids were gradually stopped. With 36 months of follow-up since she was referred to our department (ie, 144 months since disease onset), no relapse occurred.

Discussion and Literature Review

AAPOX syndrome is a type of non-Langerhans histiocytosis (type II) and is characterized histopathologically by a periocular infiltration of foamy histiocytes and Touton giant

TABLE 2. Histopathologic Features in AAPOX Patients

	Patient 1	Patient 2	Patient 3
Histopathologic features of ocular adnexa* in AAPOX patients			
Touton giant cells	Yes	Yes	Yes
Foamy histiocytes	Yes	Yes	Yes
Lymphoplasmacytic Infiltrate	Yes	Yes	Yes
Fibrosis			
Storiform	No	No	No
Collagen	Yes	Yes	Yes
Phlebitis	No	Yes	Yes
Eosinophilia	No	No	No
IgG4 + plasma cell counts in involved organs of AAPOX patients			
Ocular adnexa*			
IgG4 + cells/HPF	40	>100	>100
IgG4+/IgG + cells ratio (%)	>50	>50	>50
Others sites	Cheek	Salivary glands	Salivary glands
IgG4 + cells/HPF	40	>100	80
IgG4+/IgG + cells ratio (%)	>50	>50	>50
Lymphadenopathies			
IgG4 + cells/HPF	NA	45	NA
IgG4+/IgG + cells ratio (%)	NA	>50	NA

AAPOX = adult onset asthma and periocular xanthogranuloma, HPF = high power field, NA = not available.

* Ocular adnexa denotes palpebral connective tissue (Patient 1) and the lacrimal gland with the surrounding palpebral tissue (Patients 2 and 3).

cells. Both are CD68 and CD1a positive, and S100 negative on immunostaining.[3] Less than 30 cases of patients with AAPOX syndrome have been reported in the literature. This rare disease of unknown etiology affects adults aged between 22 and 74 years, with a male to female ratio of 2:1.[2] The mechanisms underlying AAPOX are poorly understood. AAPOX is a systemic disease involving orbits, lungs, and lymph nodes.[2] In a recent study using FDG PET/CT, one patient displayed FDG uptake in eyelids, lacrimal glands, perirectal fat and in intrathoracic and inguinal lymphadenopathies.[4] The lymph node biopsy showed a benign reactive follicular lymphoid hyperplasia as it has previously been reported in AAPOX patients with lymphadenopathies.[1,4] Chronic rhinosinusitis, mild eosinophilia, and elevated serum IgE level are frequent features in AAPOX patients.[10] Corticosteroids are proposed as a first line treatment because low dose may induce a durable response in patients with AAPOX.[4] Methotrexate could be an efficient corticosteroid sparing agent when AAPOX syndrome relapses.[10,11]

We report 3 consecutive cases of AAPOX patients that satisfy the comprehensive clinical diagnostic criteria for IgG4-RD. Two of them (Patients 2 and 3) met the requirements for the diagnosis of definite IgG4-RD and even fulfilled the more stringent criteria proposed in the consensus statement on the pathology of IgG4-RD.[7,9] Ocular adnexal biopsies for these 2 patients disclosed more than 100 IgG4-positive plasma cells per high-power field (hpf), the threshold used for lacrimal gland involvement. In both cases, the IgG4-positive plasma cell infiltrate reached this cutoff value in the lacrimal gland and not in the palpebral tissue where plasma cells and follicles are sparse.

Patient 1 had an IgG4 serum level of 1 g/L and therefore, based on histologic features, only met the requirement for the diagnosis of a probable IgG4-RD according to the comprehensive clinical diagnostic criteria for IgG4-RD.[9] The IgG4-positive plasma cell infiltration did not reach the cutoff of 100 per hpf in the eyelids in Patient 1 as in the case of Patients 2 and 3, but no lacrimal gland biopsy was available in this patient. Nevertheless, the ratio of IgG4-positive to IgG-positive plasma cells was higher than 50% for Patient 1 and a left cheek mass was shown to be an additional localization of IgG4-RD as required by the consensus statement to diagnose a probable IgG4-RD. To our knowledge, no study has focused on the presence of IgG4 + plasma cell infiltration in the palpebral tissue.[7,12] Typical storiform fibrosis and obliterative phlebitis were not found in our patients. As previously reported in case series of ocular adnexal IgG4-RD and as stated in the consensus statement, typical storiform fibrosis and obliterative phlebitis are relatively uncommon in cases of IgG4-related orbitopathy.[7,12–14]

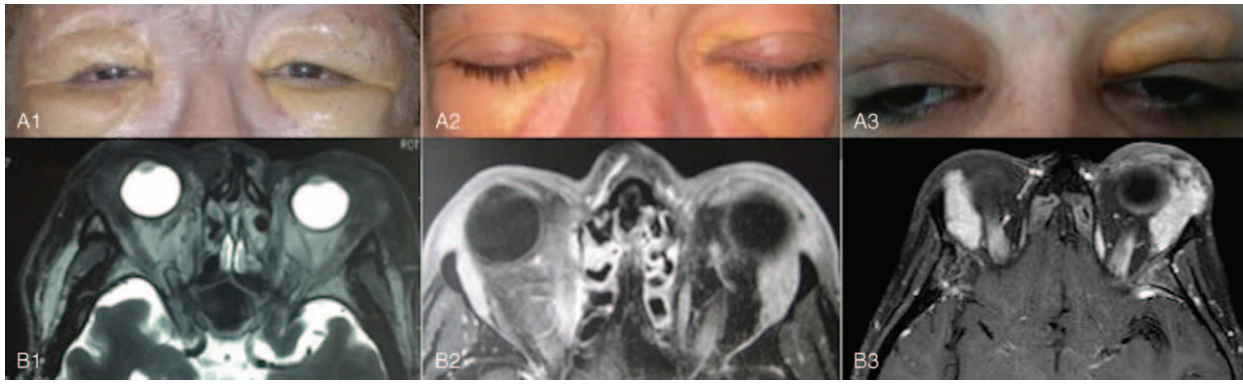

FIGURE 1. Eyelid involvement in AAPOX patients. Yellow swelling of eyelids (panel A) of Patient 1 (A1), Patient 2 (A2), and Patient 3 (A3). Orbital MRI images (panel B) of Patients 1, 2, and 3 revealed hypertrophy (B1, axial T2-weighted MR scan) and enhancement (B2 and B3, postcontrast axial T1-weighted MR images) of the eyelids and lacrimal glands.

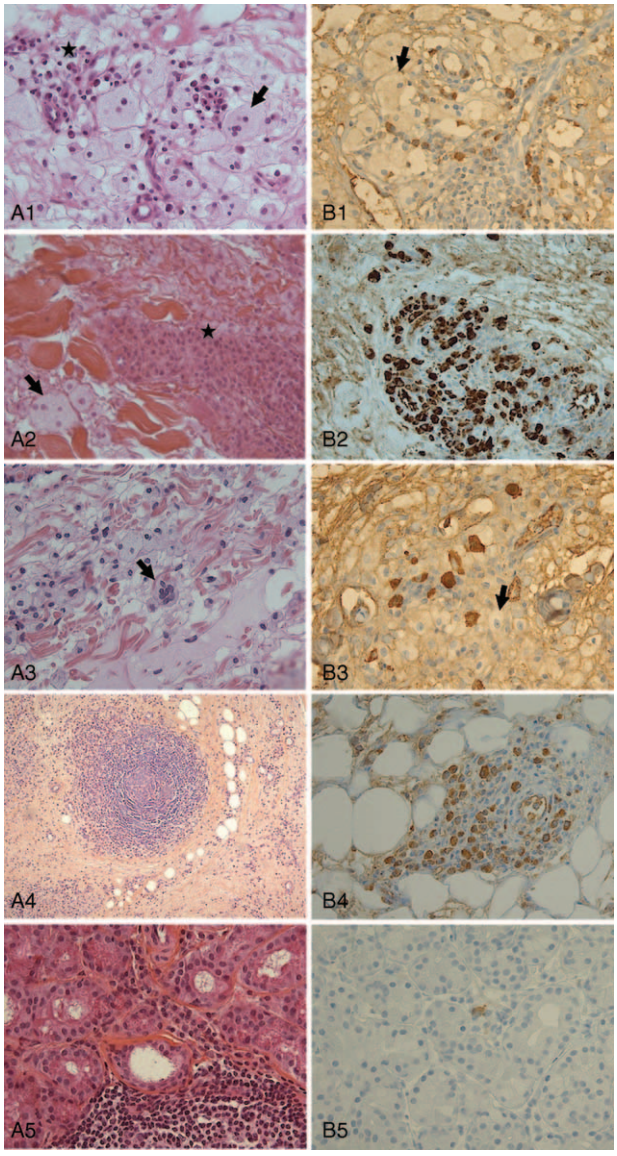

FIGURE 2. Histopathologic findings of ocular adnexal biopsy in AAPOX patients. HES stain (panel A) and IgG4 immunostaining (panel B) of Patient 1 (A1 and B1), Patient 2 (A2 and B2), Patient 3 (A3 and B3), of a patient with confirmed IgG4-RD orbitopathy (A4 and B4) and of a patient with nonspecific dacryoadenitis (A5 and B5). Follicular lymphoid hyperplasia, plasma cell infiltrate (stars), and foamy histiocytes with giant multinucleated cells or Touton cells (arrows) were found on biopsy of Patients 1, 2, and 3 (A1, A2, and A3). IgG4 immunostaining on ocular adnexal tissue revealed IgG4-positive plasma cells admixed with foamy histiocytes and/or Touton giant cells in all AAPOX patients (B1, B2, and B3). By comparison, lymphoplasmacytic infiltrate (A4) with increased number of IgG4-positive plasma cells (B4) is shown in a patient with confirmed IgG4-orbitopathy we previously reported.[8] Lymphocytic infiltrate without foamy histiocytes or multinucleated giant cells (A5) and negative IgG4 immunostaining (B5) are shown in a patient with nonspecific dacryoadenitis. All slides are at ×400 magnification.

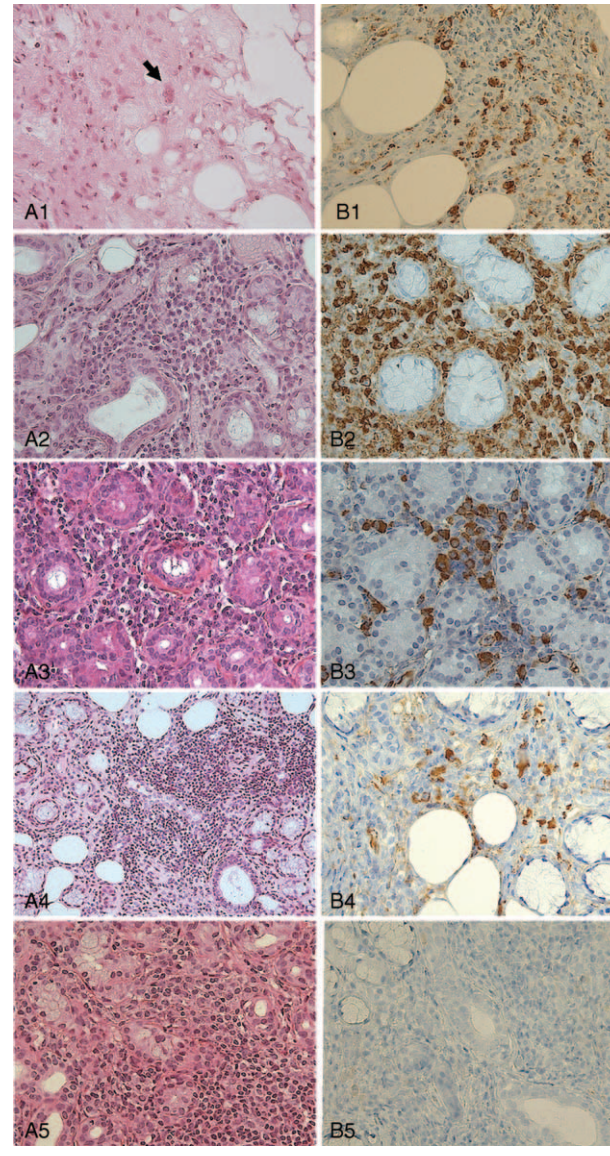

FIGURE 3. Histopathologic findings of biopsy from others sites in AAPOX patients. HES stain (panel A) and IgG4 immunostaining (panel B) performed on different tissues: the cheek for Patient 1 (A1 and B1) and minor salivary gland for Patient 2 (A2 and B2), and Patient 3 (A3 and B3). Samples from a patient with confirmed IgG4-orbitopathy (A4 and B4), and a patient with Sjögren syndrome (A5 and B5) were used as positive and negative controls, respectively. Follicular lymphoid hyperplasia and plasma cells infiltration were found for all patients (A1, A2, A3, A4, and A5). Xanthogranulomatous reaction with Touton giant cells (arrow) is shown on the subcutaneous tissue biopsy of the cheek of Patient 1 (A1). IgG4 immunostaining was strongly positive on plasma cells for Patients 1, 2, and 3 (B1, B2, and B3) and for the patient with confirmed IgG4-RD (B4)[8] but was negative for the patient with Sjögren syndrome (B5). All slides are at ×400 magnification.

Remarkably, AAPOX patients shared other clinical, serological, and morphological features with patients diagnosed with IgG4-RD. As frequently reported in patients with IgG4-positive Mikulicz disease, all of our AAPOX patients had allergic manifestations such as an increased serum IgE level and/or sinusitis and asthma.[5,15] Masaki et al found that allergic rhinitis was significantly more common in IgG4-positive Mikulicz patients than in typical SS (40.6% vs. 6.5%; $P < 0.001\%$). In comparison, the incidence rate in the general Japanese population varies from 5% to 10%.[5] We previously evaluated FDG PET/CT in AAPOX patients and found FDG uptake of organs usually involved in IgG4-RD, that is, lacrimal glands, lymph nodes, and perirectal fat, the latter 2 being asymptomatic.[4] As has been shown in case of IgG4-RD, FDG PET/CT was useful for the staging of the AAPOX syndrome.[16] Corticosteroids are typically the first line of therapy for both IgG4-RD and AAPOX syndrome. As reported in the majority of patients with IgG4-RD, corticosteroids were initially effective in our AAPOX patients but disease flares sometimes occurred. As in Cases 2 and 3, methotrexate can be successfully used as a corticosteroid sparing agent in IgG4-RD.[17]

Roggin et al described for the first time an association between lymphoplasmacytic sclerosing pancreatitis, a well-recognized IgG4-RD, and AAPOX in 1 patient. This patient had an elevated serum IgG4 level.[18] However, no IgG4 immunostaining was realized on palpebral or pancreatic biopsy to confirm IgG4-RD. Recently, Verdijk et al[19] reported that raised numbers of IgG4-positive plasma cells are a common histopathological finding in AAPOX syndrome. Two AAPOX patients had a ratio of IgG4+/IgG + plasma cells of more than 40% but a threshold of only 50 IgG4-positive plasma cells per hpf was used.[7,19] Unfortunately, the serum IgG4 level had not been assessed for these 2 patients. One of them had a 1-sided salivary gland enlargement. But no histologic evaluation was performed to confirm other organ involvement as is usually requested by the consensus statement on the pathology of IgG4-RD when histological features are not highly suggestive of IgG4-RD.

According to the comprehensive diagnostic criteria for IgG4-RD, the diagnosis of IgG4-RD relies both on an elevated serum IgG4 concentrations and on an IgG4 + plasma cells infiltration, but it also necessitates differentiating IgG4-RD from other disorders that can present an IgG4-positive plasma cell infiltration.[9,20] The known diseases for which an IgG4-positive plasma cell infiltration has been reported to occur, including lymphoma, Castleman disease, sarcoidosis, cancer, or vasculitis have been excluded in our patients based on clinical presentation, biological, radiological, and histological features. Unlike these well-defined conditions, AAPOX is a poorly characterized syndrome and its pathophysiology is not well known. AAPOX syndrome and IgG4-RD share some clinical, biological, pathological, morphological features, and treatment outcomes. None of our patients had recurrent infections or other clinical findings associated with immune deficiency. All patients had extended follow-up of several years without any clinical or histological features suggestive of lymphoma and with good clinical, biological, and morphological response to treatment with corticosteroids (and low dose methotrexate in 2/3 patients). Systemic symptoms associated with multicentric Castleman disease were not present in our patients. AAPOX syndrome could be considered an IgG4-RD differential diagnosis presenting as a xanthogranulomatous disease with accompanying IgG4-positive plasma cell infiltration or, as the data we present suggest, AAPOX syndrome could be part of the spectrum of IgG4-RD. Further studies are needed to specify the link between AAPOX and IgG4-RD.

CONCLUSIONS

With these 3 consecutive cases of AAPOX patients who fulfill the criteria for IgG4-RD, we provide clear evidence supporting the theory that AAPOX and IgG4-RD are strongly linked.

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