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CLINICAL CASE

Enfermedad relacionada con IgG4 y Linfoma MALT retroorbitario. Una patología infrecuente

Disease related to IgG4 and retro orbital MALT Lymphoma. A rare disease

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What do we know about the subject matter of this study?

Pediatric cervical lymphadenopathies are common with etiologies that include infections, reactive lymphadenopathies, malignant neoplasms, and benign processes such as IgG4-related disease (IgG4-RD), angiolymphoid hypertrophy with eosinophilia (ALHE), Kimura disease (KD), and Sjögren's syndrome.

What does this study contribute to what is already known?

We describe a pediatric case of IgG4-RD, a multisystem fibroinflammatory disease characterized by infiltration of IgG4-bearing plasma cells, eosinophilia, and elevated IgE, which progressed to MALT lymphoma. In addition, we emphasize the importance of long-term follow-up of this rare pathology.

Abstract

IgG4-related disease (IgG4-RD) is a chronic benign neoplastic process, clinically heterogeneous, of unknown etiology and low occurrence, with specific histologic and immunocytochemical characteristics, predominantly affecting adults. Exceptionally, it may progress to lymphoma. **Objective**: To report a pediatric patient with IgG4-RD and emphasize the importance of long-term follow-up, given its potential evolution towards malignancy. **Clinical Case:** We present a 6-year-old girl who presented with a one-year history of asymmetric bilateral enlargement of cervical lymph nodes and salivary glands, which progressed rapidly over the past two months with no associated symptoms. Malignant neoplasms were ruled out, and spontaneous regression occurred. Seven years later, she presented bilateral cervical lymphadenomegaly with left predominance, parotid swelling, and left eyelid edema. Histopathological and immunohistochemical analysis of the lymph node biopsy and serum IgG4 levels confirmed the diagnosis of IgG4-RD. Treatment with oral corticosteroids followed by methotrexate was started, with positive response over 2 years. However, during methotrexate therapy, lym-

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ph node, glandular, and eyelid involvement recurred, with left proptosis. The MRI and biopsy of the retrobulbar mass revealed a mucosa-associated lymphoid tissue lymphoma, which was treated with radiotherapy and chemotherapy until remission. **Conclusion:** Long-standing head and neck tumor processes may consist of benign proliferative diseases, such as IgG4-RD, which may occasionally progress to lymphoma.

Introduction

The differential diagnosis of neck lymphadenopathy and pediatric facial glandular hypertrophy includes viral or bacterial infections, reactive lymphadenopathy without specific etiology, malignant hematopoietic neoplasms, metastases of malignant solid tumors and benign neoplasms such as IgG4-related disease (IgG4-RD), angiolymphoid hypertrophy with eosinophilia (ALHE), Kimura disease (KD), and Sjögren's syndrome[1,2]. IgG4-RD, ALHE, and KD are infrequent, with similar presentation in the head and neck[3-5]. Laboratory tests, imaging, histology, and immunohistochemistry allow establishing the differential diagnosis[6-8].

IgG4-RD is a systemic fibro-inflammatory disease, identified this century by Japanese researchers, characterized by infiltration of organs and tissues by IgG4-bearing plasma cells[3]. It is expressed by elevated levels of IgG4-positive plasma cells, associated with eosinophilia and high serum IgE. It can occur in any organ. Syndromes of single-organ involvement have been described, such as Riedel's thyroiditis, Küttner's tumor (sclerosing sialadenitis of the mandibular gland), Mikulicz's disease (simultaneous submandibular, parotid, and lacrimal involvement), Ormond's disease (retroperitoneal fibrosis), and autoimmune pancreatitis type 1[6]. The epidemiology is unclear. Nearly 80% of reported cases are in Japanese patients, with an average age at diagnosis of around 60 years and a male predominance[2,3]. In adults, progression to lymphoma has been described[9].

Its presentation in the pediatric age is infrequent. A systematic review reported by Karim et al. found 25 pediatric cases[10], with a mean age of 13 years (range 22 months to 17 years) and 64% were girls. In addition, IgG4-related orbital disease (44%) and autoimmune pancreatitis type 1 (5%) predominated, unlike cholangitis, pulmonary involvement, and lymphadenopathy which were less frequent[10]. We found no reports of IgG4-RD in South America, nor pediatric reports of progression to lymphoma. The objective is to report this infrequent pathology in a pediatric patient and to emphasize the importance of long-term follow-up, given its possible progression to malignancy.

Clinical Case

A 6-year-old girl of Hispanic descent, without consanguinity or exposure to toxic environmental factors, living in an urban area and previously healthy, consulted in an outpatient medical office due to a 12-month history of bilateral painless cervical lymphadenopathy, which had worsened over the last two months. She had no history of fever, weakness, or weight loss. No personal or family history of morbidity.

Physical examination revealed multiple, painless palpable cervical lymph nodes up to 2.0 x 3.0 cm, not adherent to deep planes, bilateral, predominantly on the left side. No adenopathies in other locations, skin lesions, visceromegaly, or general or nutritional compromise were observed.

The soft tissue ultrasound revealed multiple bilateral hypoechoic cervical lymph nodes, both superficial and deep, ranging from 1.0 to 3.5 cm in diameter, located in the jugular, submandibular, and intraparotid regions, without signs of periadenitis. The thyroid gland appeared normal. An abdominal ultrasound ruled out visceromegaly and retroperitoneal lymphadenopathy. The biopsy of a lymph node and adipose tissue revealed reactive lymphoid hyperplasia. The chest X-ray was normal. Therefore, no additional studies or specific therapy were deemed necessary, and the lymphadenopathy resolved spontaneously.

Seven years later, the patient, now 13 years old, returned for evaluation due to a rapid enlargement in the left side of cervical, parotid, and submandibular adenopathies, which she had noticed over three months.

Physical examination and cervical ultrasound confirmed the signs described. Abdominal ultrasound and CT scan of the brain and sella turcica were normal. MRI of the head and neck corroborated the tumorous lesions in the cervical lymph nodes and salivary glands, with no signs of bone deterioration.

Laboratory tests showed a leukocyte count of 10,000 per mm^3 (normal range (NR) 4,000 - 10,000 per mm^3), eosinophilia 2,220 eosinophils per mm^3 (NR 0-200 per mm^3), serum IgE levels ranged from 213 IU/ml to 2,489 IU/mL (NR <100 IU/ml). Serum concentrations measured by turbidimetry (SPA Plus®, The Binding Site, UK) of IgG2 were 660.7mg/

dl (NR 100-455 mg/dl) and IgG4 440 mg/dl (NR 3.7-136 mg/dl). Acute phase reactants and other immunological tests, including infection serology, were normal (Table 1).

Cervical biopsy showed subcutaneous, fibroadipose, and skeletal muscle tissue, with marked fibrosis and chronic inflammatory infiltrate, with lymphoid follicles, mature and activated lymphocytes, numerous eosinophils, plasma cells, and mild vascular proliferation (Figures 1 a and b). No evidence of lymphoproliferative disease.

Immunohistochemical studies were performed on an automated staining system (BenchMark ULTRA, Ventana Medical Systems, Inc). Immunophenotypic findings, with CD5 [clone SP19], CD20 [clone L26], and BCL2 [clone 124], revealed the reactive nature of the lymphoid infiltrate. No Hodgkin or Reed-Sternberg cells were found with CD30 [clone BER-H2], CD15 [clone MMA], and PAX-5 [clone SP34]. Plasma cells with polyclonal IgG and IgG4 antibodies were increased in number and proportion of IgG4-positive (IgG4+) plasma cells, exceeding 50 IgG4+ cells per high-power field, and an IgG4+/IgG+ ratio greater than 50% (Fig. 1c and d). The morphological and immunohistochemical features were consistent with IgG4-RD.

Table 1. Laboratory tests requested in the evaluation of 13-year-olds in the context of studying cervical lymphadenopathy

Examination	Result
Biochemical Profile	Values within normal range
Liver Profile	Values within normal range
Renal Profile	Values within normal range
ESR	4 mm/hour (Reference Value: 1 – 24 mm/hour)
Ferritin	Normal
C3	Normal
C4	Normal
ANA	Negative
ENA Profile	Negative
HIV	Non-reactive
HTLV1	Non-reactive
IgM/IgG EB	Negative/Positive
IgM/IgG BH	Negative/Positive

ANA: antinuclear antibodies; ENA: extractable nuclear antigens; EB: Epstein-Barr; BH: *Bartonella henselae*.

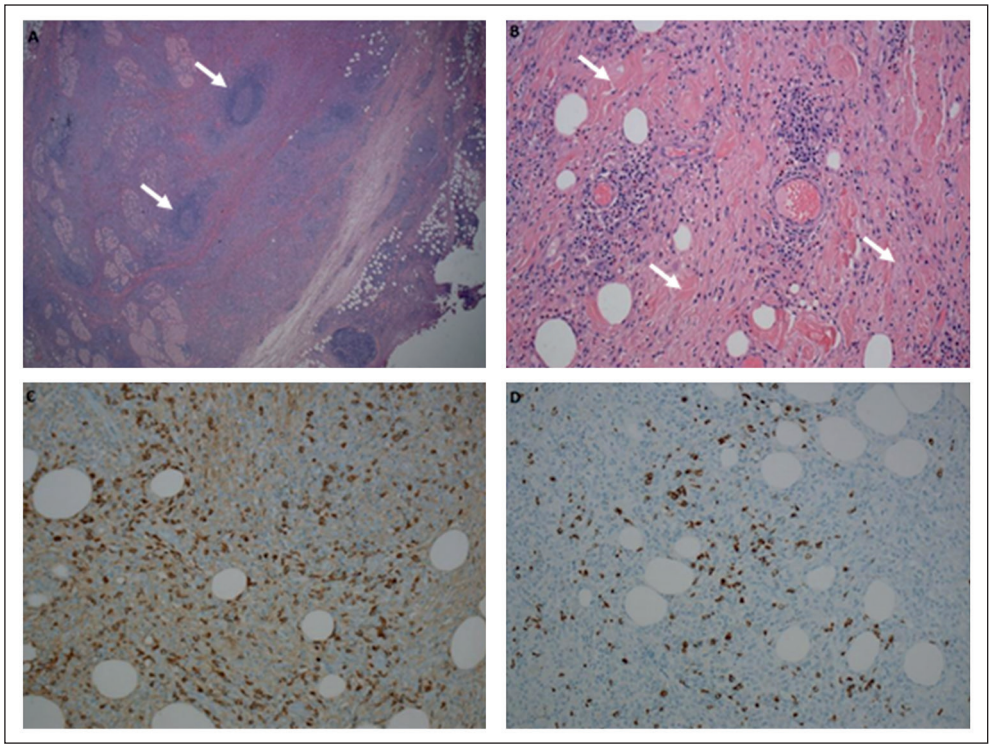

Figure 1. (a) Fibroadipose tissue and skeletal muscle with fibrosis and chronic inflammatory process, including lymphoid follicles (arrows). **(b)** Eosinophilic infiltrate intermixed with plasma cells visible in the fibrotic areas, with eosinophilic collagen deposits and bundles (arrows). Immunohistochemical study (where the cells positive for the used antibody show brown staining) for IgG **(c)** and IgG4 **(d)**, evidences an expression ratio of IgG4 to IgG of approximately 50%.

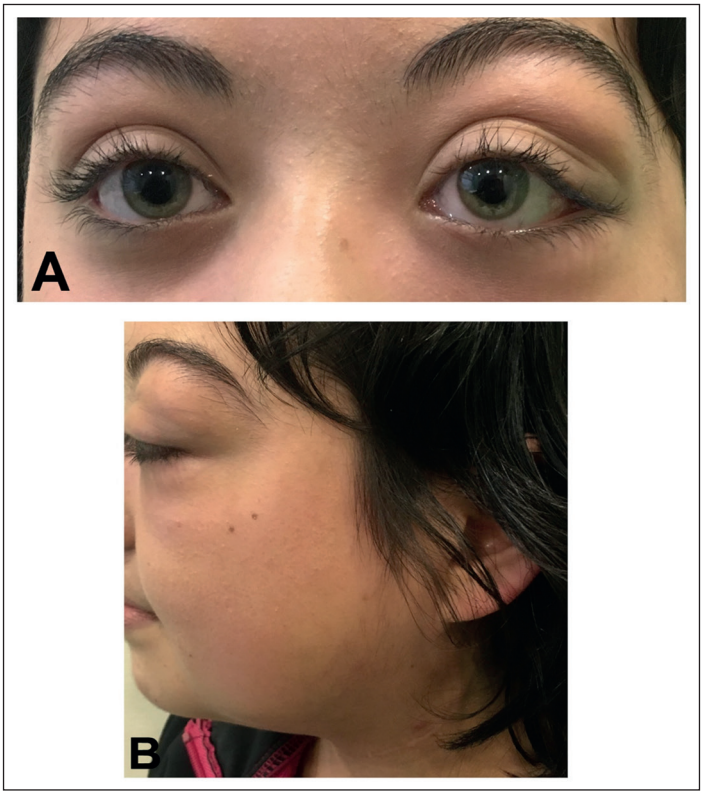

Figure 2. Clinical photographs of the patient. **(a)** Photo showing the increase in volume of the left upper and lower eyelids, associated with mild ocular proptosis. **(b)** Lateral photograph showing the masses of the face and neck corresponding to the increase in volume of the left submandibular and parotid glands, as well as left cervical lymphadenopathy.

A left superficial partial parotidectomy and submandibular gland resection were performed. The resection included soft tissues of the submandibular region, superficial left parotid tissue, and ipsilateral lymph nodes, with findings consistent with previous biopsy.

One month after surgery, the patient started prednisone at 1mg/k/day, with rapid improvement. However, attempts to decrease the corticosteroid dose were unsuccessful, leading to cushingoid facies and purple stretch marks. Oral methotrexate was prescribed, later switched to subcutaneous administration at 15 mg/m^2 weekly, achieving corticosteroid discontinuation and clinical stability for 2 years.

At the age of 16, 10 years after the onset of symptoms and 2 years of immunosuppressive treatment, she noted an increase in superior palpebral volume, mild left proptosis, and recurrence of cervical and facial masses (Figures 2a and b). Serum concentrations of IgG2 and IgG4 were slightly increased at 500 mg/dl (NR 64-495 mg/dl) and 185 mg/dl (NR 11-157 mg/dl), respectively. An orbit CT scan revealed a retro-orbital mass without bone involvement. The biopsy of this mass showed fibroadipose tissue extensively infiltrated by atypical lymphoid proliferation with nodular/follicular and diffuse pattern, remnant lymphoid follicles, small cells with irregular, hyperchromatic nuclei, and scant cytoplasm, plasmatic differentiation, and few large activated lymphoid cells (Figure 3a).

The immunohistochemical study revealed B-cell lymphoid neoplasm, with expression of CD20 [clone L26], CD43 [clone 124] (Figures 3b and c), and BCL2 [clone 124], with lambda light chain restriction [clone Lamb 14] (study of Kappa [L1C1] and Lambda immunoglobulin light chains) (Figures 3d and e). The tumor plasma cell population, with lambda chain restriction, showed overexpression of IgG4 [polyclonal], of the same intensity and proportion as in previous biopsies (Figure 3f). The proliferative index of the tumor lesion, assessed using KI67 [clone SP6], ranged from 10-20%. The morphological and immunohistochemical findings were compatible with extranodal marginal zone B-cell lymphoma of MALT type (MALT lymphoma).

The adolescent was referred to an oncology center for radiotherapy and chemotherapy, which she completed without adverse effects. After 3 years in remission, she presented an outbreak of adenomegaly and proptosis attributed to IgG4-RD, therefore corticosteroids were restarted until further evaluation.

Discussion

We presented a clinical case of IgG4-RD of glandular phenotype, progressive cervical adenomegaly, and ocular involvement, evolving into MALT lymphoma. IgG4-RD is a systemic fibroinflammatory disease, clinically described and named by those who reported it in syndromes affecting a single organ, defining the specific signs and symptoms of the involved organs or their association: thyroid, salivary glands, eye, and pancreas, at that time without a demonstrated etiology[6]. At the beginning of the 21st century, Japanese researchers identified a relationship between elevated levels of IgG4 plasma cells, eosinophilia, and high serum IgE, with the previously described symptoms. This allowed the definition of IgG4-RD, which facilitated the unification of diagnostic criteria, study methods, and the incorporation of new phenotypes[2,3,6,10-11].

Between 2000 to 2014, Stone analyzed in some publications the diagnostic complexity of IgG4-RD[12]. According to the review, a recommended diagnostic criterion was elevated serum IgG4, with a value higher than 135 mg/dl, or 4 to 6 times higher than the upper limit of normal. However, high IgG4 is not specific to this pathology and recent studies have pointed out its limitations[13]. Some studies that evaluated the total

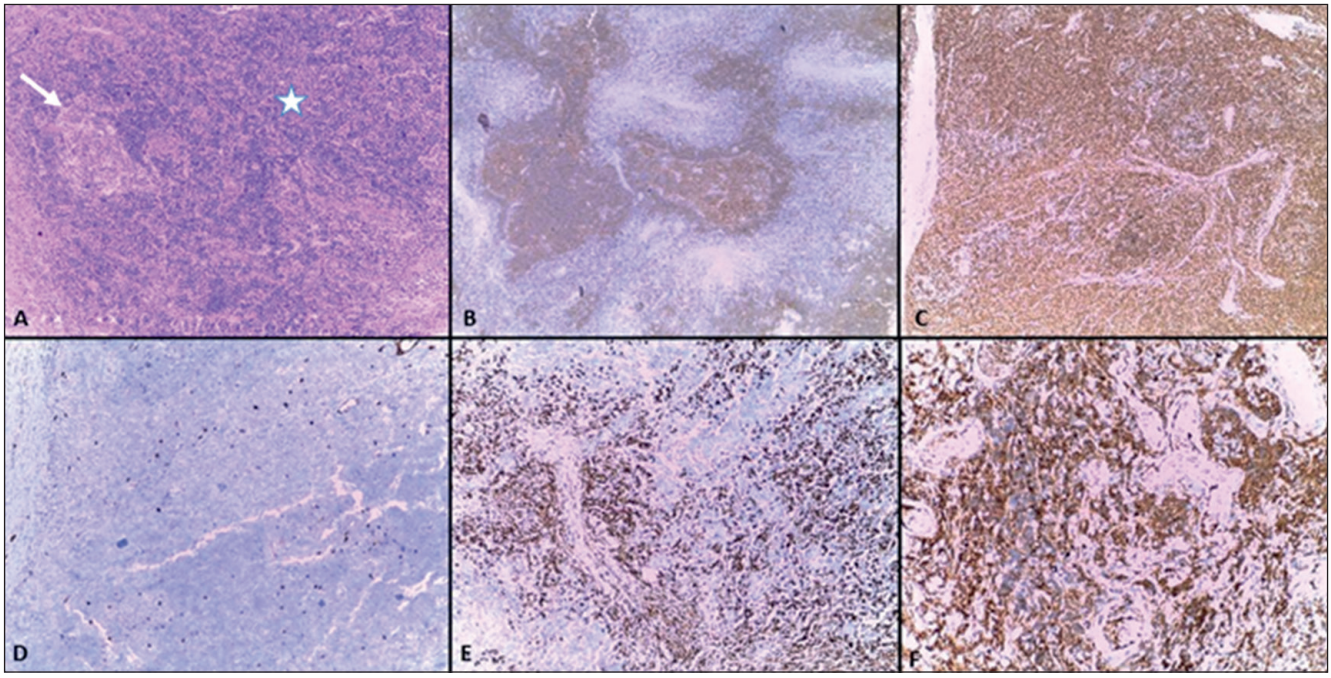

Figure 3. Fibroadipose tissue extensively infiltrated by an atypical lymphoid proliferation of nodular/follicular and diffuse pattern, with remaining lymphoid follicles (arrow) and the presence of small cells arranged in a diffuse pattern (star) **(a)**. The immunohistochemical study (where the cells positive for the used antibody show brown staining) reveals that this population is of B lymphoid phenotype, with CD20 expression [clone L26] **(b)**, co-expression of BCL2 [clone 124] **(c)** and restriction of light chain Lambda [clone Lamb 14] (study of light chains of Kappa [L1C1] and Lambda immunoglobulins) (Fig. **d** and **e**, respectively). The population of tumor plasma cells, with Lambda light chain restriction, also showed overexpression of IgG4 [polyclonal], as in the previous biopsy **(f)**.

IgG4/IgG ratio indicate that it is usually less than 5%[13]. In our case, serum IgG4 levels were 4 times higher than normal, and the IgG4/IgG ratio was greater than 50%. The presence of specific autoantibodies has not been identified in patients with IgG4-RD; however, it has been reported that approximately 30% of patients have positive antinuclear antibodies and 20% have a positive rheumatoid factor. Identifying specific autoantibodies such as anti-Ro/SSA, anti-DNA, and ANCA should suggest another autoimmune condition such as Sjögren's syndrome, systemic lupus erythematosus, or granulomatosis with polyangiitis[13,11].

In 2014, Deshpande reported the histopathological consensus of IgG4-RD[14], describing the main morphological signs observed in this entity, independent of the anatomical area affected, including dense lymphoplasmacytic inflammatory infiltrate, with the variable eosinophilic component, associated with storiform fibrosis, and signs of obliterative/non-obliterative phlebitis. Peripheral blood plasmablasts concentrations, identified through flow cytometry focusing on CD19 low, CD38 +, CD20-, and CD 27+ cells, may be more reliable than IgG4 for diagnosis and longitudinal patient follow-up. However, this cytometry is not yet available in Chile[2,10-13].

An international multidisciplinary group of 86 physicians from North America, Europe, and Asia, gathered under the wing of the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) developed, validated, and published in 2019 a set of classification criteria for IgG4-RD[15]. They included 1879 patients both confirmed and mimic cases, reinforcing the low incidence and prevalence of this pathology. They identified clinical, serologic, radiologic, pathologic, and disease-specific features as exclusion criteria, outlined inclusion criteria, and proposed a step-by-step classification. Although this classification is aimed at standardizing criteria for research, our case aligns with previous and recently agreed upon clinical and diagnostic support criteria.

Although IgG4-RD is a benign tumor, treatment is recommended except in localized and oligosymptomatic forms because, if it is not treated, it can cause irreversible organic damage[3]. Glucocorticoids are the first-choice drugs. Treatment with prednisone at 1-2 mg/k/d is usually effective quickly and should be maintained for 2-4 weeks. In our case, we attempted to slowly decrease the prednisone dose considering the adverse effects, but the patient relapsed, as has been

reported, thus we used steroid-sparing agents[3,10,11,16]. As it was available, we used methotrexate while monitoring serum IgG4, with favorable clinical and serologic response. The last serum IgG4 was 185.5 mg/dl (NR 11-157 mg/dl). Ten years after symptom onset and two years after diagnosis, still on methotrexate, we observed orbital clinical reactivation. While we were considering the use of Rituximab, due to positive clinical results reported[16], the biopsy of the retro-orbital tissues showed MALT lymphoma, a situation reported in adults but, to our knowledge, not yet reported in pediatric patients[2,9,11].

A differential diagnosis of IgG4-RD is ALHE, initially raised based on clinical and first histopathologic report, without immunohistochemistry. ALHE has been reported in all races and in both sexes, characterized by single or multiple angiomatous lesions, located on the scalp and/or face, rarely elsewhere[4,7,17]. Reviewing the scientific literature, we identified 14 pediatric cases[4,7,17-19] including four cases with ophthalmologic involvement (7,18 and 19). This pathology appears predominantly during the 3rd or 4th decade of life, more frequent in females. Normal total serum IgE and eosinophilia less than 10% are described. Our case had no visible skin lesions and both IgE and blood eosinophil values did not support the initial diagnosis.

Another differential diagnosis is KD, a benign chronic inflammatory disease of unknown etiology. It is postulated that KD is probably an autoimmune or allergic response that occurs almost exclusively in middle-aged Asian men, although occasionally reported in other ethnicities. Reviewing pediatric publications, we identified 55 cases, predominantly in Asians or those of Asian ancestry[8,21,22] [9 cases in children ref 22; personal communication with Dr. Kim]. Chen described that KD usually appears with subcutaneous masses in the head and neck, marked eosinophilia, and elevated serum IgE, without systemic symptoms[8]. Its treatment is similar to ALHE and IgG4-RD.

Upon reevaluating our pediatric female patient, we reassigned the diagnosis to IgG4-RD based on her eosinophilia, elevated IgG4 levels, and histological and histochemical findings confirming immunoreactivity to IgG and IgG4, despite the absence of Asian ancestry.

Conclusions

We present a pediatric case of IgG4-RD with nodal and ophthalmic phenotype that later progressed/evolved to MALT lymphoma, aiming to provide clinical insights for the suspicion and confirmation of IgG4-RD in this age group. We consider within the differential diagnosis ALHE and KD, rare benign neoplastic pathologies that share clinical features. We emphasize the importance of long-term follow-up to detect and treat hematopoietic malignancy on time, considering the association of IgG4-RD with lymphoma, described in adults and confirmed in this report.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the parents (tutors) of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author. Authors state that the information has been obtained anonymously from previous data.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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