Chronic sclerosing sialadenitis IgG4-related in a boy with recurrent parotitis: a case report

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Chronic sclerosing sialadenitis IgG4-related in a boy with recurrent parotitis: a case report

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Abstract

Background
IgG4-related diseases are a group of immune-mediated diseases characterized by a lymphoplasmacytic infiltrate with a prevalence of IgG4-positive plasma cells, storiform fibrosis, obliterative phlebitis. Autoimmune pancreatitis, sialadenitis, dacryoadenitis and retroperitoneal fibrosis are the most frequent manifestations. IgG4-related sialadenitis usually affects submandibular glands and is very rare in children. We report here a case of an unexpected diagnosis of IgG4-related sialoadenitis in a boy previously diagnosed as affected by juvenile recurrent parotitis.

Case presentation
A six-year old boy presented to our centre with left parotid swelling about 4x3 cm, tender, soft in consistency, with the overlying skin red and warm. He had low-grade fever and a mild enlargement of left cervical lymph nodes. In the last two years he had five episodes of parotitis and a diagnosis of juvenile recurrent parotitis.. The general conditions were good, and the remainder of the physical examination was normal. At the ultrasonography left parotid was enlarged, inhomogeneous, with a colliquated intraparotid lymph node and no evidence of sialolithiasis. Laboratory tests were normal, except for an increase of white blood cells and positivity for IgM and IgG anti-VCA, with anti-EBNA e anti-EA I negative. The patient was treated with cephalosporins and azitromycin, but after 10 days the parotid became fluctuating and the patient underwent to drainage and biopsy of the gland. He was discharged after 3 days of observation, without any complications, and treated with a further course of cefpodoxime and betametasone, with a good clinical response.
Investigations for aerobic and anaerobic bacteria, mycobacteria and Bartonella on the pus were negative. Histology showed marked fibrosis and histiocytic and lymphoplasmacellular infiltration. The plasma cells were polyclonal and mostly expressed IgG4 subclass immunoglobulins.
The final diagnosis was chronic sclerosing sialadenitis IgG4-related in recurrent parotitis and recent EBV infection.

Conclusions.
The interest of this case comes from the rarity of IgG4-related sialadenitis in children. It is not possible to argue with certainty that the previous episodes of parotitis were manifestations of a IgG4-related disease, due to the lack of histological data. Serum IgG4 in our patient were normal, as described in literature in 30% of cases.

Keywords
IgG4-related disease
chronic sclerosing sialadenitis
juvenile recurrent parotitis
case report

Background

The term IgG4-related disease (IgG4-RD) refers to a group of pathologies known for a long time and previously considered as single-organ diseases [1,2]. IgG4-RD share the same histology features: a lymphoplasmacytic infiltrate with a prevalence of IgG4-positive plasma cells, storiform fibrosis, obliterative phlebitis[3,4]. The majority of patients have high serum levels of IgG4 [5,6], but the diagnosis is based on the histological picture.

Autoimmune pancreatitis, sialadenitis, dacryoadenitis and retroperitoneal fibrosis are the most frequent manifestations of IgG4-RD. The pathogenesis is immune-mediated, with a central role of T-lymphocytes, whereas IgG4 do not seem responsible for the tissue damage [7,8]. The natural history, without treatment, is the evolution towards advanced fibrosis, atrophy and loss of function.

In the IgG4-related sialadenitis, submandibular glands are usually involved, whereas parotid glands are rarely affected [9,10]. Xerostomia is a common evolution of the disease.

A significant proportion of cases previously diagnosed as Miculicz's disease (dacryoadenitis and enlargement of parotid and submandibular glands) and Kuttner tumor (chronic sclerosing sialadenitis of submandibular gland) are now considered IgG4-RD.

IgG4-related chronic sclerosing sialadenitis is a rare event in children [11,12]. We report here a case of a unexpected diagnosis of IgG4-related sialadenitis in a boy previously diagnosed as affected by juvenile recurrent parotitis.

Case presentation

A six-year old caucasian boy presented to our centre with left parotid swelling and low-grade fever. He had a history of five episodes of parotitis in the last two years. No other relevant pathologies were reported. Family history negative for autoimmune diseases. During the inflammatory episodes blood tests and parotid ultrasonography were performed in a regional children's hospital. Immunological and rheumatological pathologies were excluded and a diagnosis of juvenile recurrent parotitis was made. A careful oral hygiene and a periodic otorhinolaryngological follow up were recommended.

At the visit, the parotid swelling was about 4x3 cm, tender, soft in consistency with the overlying skin red and warm. There was a mild enlargement of left cervical lymph nodes (maximum 2 cm). The general conditions were good, and the remainder of the physical examination was normal.

The differential diagnosis was between a recurrence of juvenile recurrent parotitis, infectious diseases involving parotid gland, parotid gland neoplasms.

WBC were 14400/fL with 57% neutrophils, hemoglobin and platelet counts were normal. C-reactive protein, procalcitonin, electrolytes, glucose, creatinine, transaminases were normal, as well as amylase and lipase. Serology for EBV showed positivity for IgM and IgG anti-VCA, with anti-EBNA e anti-EA IgG negative. Serologies for CMV, Bartonella, toxoplasma were negative. Mantoux TST and Quantiferon-TB were negative. IgA, IgG1, IgG2, IgG3, IgG4 serum levels were normal, whereas IgE level was increased (752 kU/L). At the ultrasonography left parotid was enlarged, inhomogeneous, with a colliquated intraparotid lymph node and a mild left latero-cervical lymphadenopathy. There was no evidence of sialolithiasis.

The patient was treated first with ceftriaxone, then with cefixime and azitromycin. During hospitalization, general conditions remained good, with intermittent low-grade fever, unchanged blood cell counts and normal C-reactive protein level, however parotid became fluctuating (figure 1) and after 10 days the patient underwent to an abscess drainage surgery of the left parotid gland. Three milliliters of pus where drained and sent for the bacteriology test, and a swelled and inflammated portion of the parotid gland was resected and sent for the histology. Reactive and swelled lymph nodes were found but not resected. Being completely evacuated, the cavity was sutured and no drainages were applied.

The patient was discharged after 3 days of observation, without any complications, and treated with a further course of cefpodoxime and betametasone, with a good clinical response.
Cultures for aerobic and anaerobic bacteria were negative as well as PCR and cultures for mycobacteria and PCR for Bartonella.
The histology showed a salivary gland fragment containing marked interlobular fibrosis and fields of dense intralobular lymphoplasmacellular infiltrate; in addition, the presence of some follicles with a reactive germinal center have been noticed. In the context of fibrosis, the periphery of the biopsy showed marked histiocytic and lymphoplasmacellular infiltration. The plasma cells had polyclonal characteristics (balanced expression of kappa and lambda light chains), and they mostly expressed class G immunoglobulins. The IgG4 subclass constituted 50-60% of total IgG and identified about 100 plasma cells / HPF in the areas of greatest expression (Figures 2-5).
The final diagnosis was chronic sclerosing sialadenitis IgG4-related in recurrent parotitis and recent EBV infection.
After surgery, the patient was treated with a course of cephalosporins and corticosteroids, with a good clinical response. Then, a strict follow up was started.
Two months after hospitalisation, the clinical conditions were good, there was no more swelling of the left parotid, pancreatic enzymes and abdominal ultrasound were normal, a panel of autoantibodies was negative.

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Discussion and Conclusions

The histological diagnosis of IgG4-RD follows the indications of the consensus statement [13] that identifies two categories, named “histologically highly suggestive”and “with probable histological features”, respectively. To allow the aforementioned categorization, at least one of the following main histological characteristics has to be present: dense lymphoplasmacytic infiltrate, storiform fibrosis,and obliterative phlebitis. The IgG4 / IgG ratio has to be at least 40%. Finally the number of plasma cells for HPF has to be counted. According to Despande et al., the diagnosis of our case was “histologically highly suggestive” (IgG4 / IgG> 40%, dense lymphoplasmacytic infiltrate and fibrosis storiform and> 100 IgG4 / HPF).
Our patient had previous various episodes parotitis diagnosed as “juvenile recurrent parotitis”.
Juvenile recurrent parotitis is a recurrent non-obstructive and non-suppurative parotid inflammation, with the higher incidence between 3 and 6 years of age. It has a benign course and usually disappear in the second decade of life.[14-16].
Various viral agents, poor oral hygiene, congenital malformations of the salivary duct, immunological defects have been sometimes related to the recurrent episodes, but the aetiology remains unknown in the majority of the cases. The possible association with a selective IgA deficiency has been described [17, 18]. There is evidence of a role of operative sialendoscopy in the treatment of the disease, however to wait and see seems reasonable, given the high rate of spontaneous remission [19].
In the present case, it is not possible to argue with certainty that the previous episodes of parotitis were manifestations of a IgG4 RD, due to the lack of histological data.
In our patient serum IgG4 were normal, whereas IgE were increased. High serum levels of IgG4 are usually described in IgG4-RD, but they can be normal in 30% of cases [6, 20-23].
The role of the recent EBV infection in the present case is not clear, as well as that of a possible bacterial super-infection, as cultures were performed after antibiotic treatment.
The first line therapy for IgG4-RD are corticosteroids, with a good response rate. Immunosuppressive agents as methotrexate, azathioprine and mycophenolate have been used in relapsed-resistant cases.[23-25], whereas rituximab has been utilized for patients resistant to both corticosteroids and immunosuppressive agents [26].
The diagnosis of IgG4-RD requires a careful follow up for the early detection of possible complications or other localisations of the disease.

In the year following the hospitalisation, the patient had two other episodes of mild tender swelling of left parotid, without fever and with normal WBC and C reactive protein levels. At the ultrasonography left parotid was enlarged and inhomogeneous, with left latero-cervical lymphadenopathy (maximum diameter 18 mm). The patient was treated successfully with a short course of amoxicillin and betamethasone without adverse events. In consideration of the good and rapid clinical response, a more prolonged treatment with corticosteroids seems so far not appropriate
A periodic surveillance for other IgG4-related clinical manifestations is currently negative.

List of abbreviations

IgG4-RD: IgG4-related disease
HPF: high-power field

Figure legends
Figure 1: Left parodid swelling before surgery
Figure 2: Interlobular fibrosis with dense lymphoplasmacellular infiltrate (hematoxylin and eosin, 10x magnification)
Figure 3: High number of plasma cells (Giemsa, 40x magnification)
Figure 4: Plasma cell with strong cytoplasmatic expression for IgG (IgG immunohistochemistry, 40x magnification)
Figure 5: Plasma cell with strong cytoplasmatic expression for IgG4 (IgG4 immunohistochemistry, 40x magnification)

Declarations

Ethics approval and consent to patecipate
The case report has been notified to the Ethics Committee of ASLTO4 on February 1th 2021.

Consent for publication
Written informed consent was obtained from the parents/legal guardians for pubblication of this case report and any accompanying images. A copy of the written consent is available for the review by the Editor-in-Chief of this journal.
Contact author for the form.

Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request, anonymously.

Competing interests
The authors declare that they have no competing interests.

Funding
Nothing to declare.

Authors' contributions
FT, supervised the patient management and wrote the manuscript. MMC and AMC contributed to the patient management, analyzed the data and discussed the paper. GOG performed surgery, contributed to the patient management and in writing the paper. FV performed the histological

analysis and contributed in writing the paper. All the Authors read and approved the final version of this manuscript.

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Figures

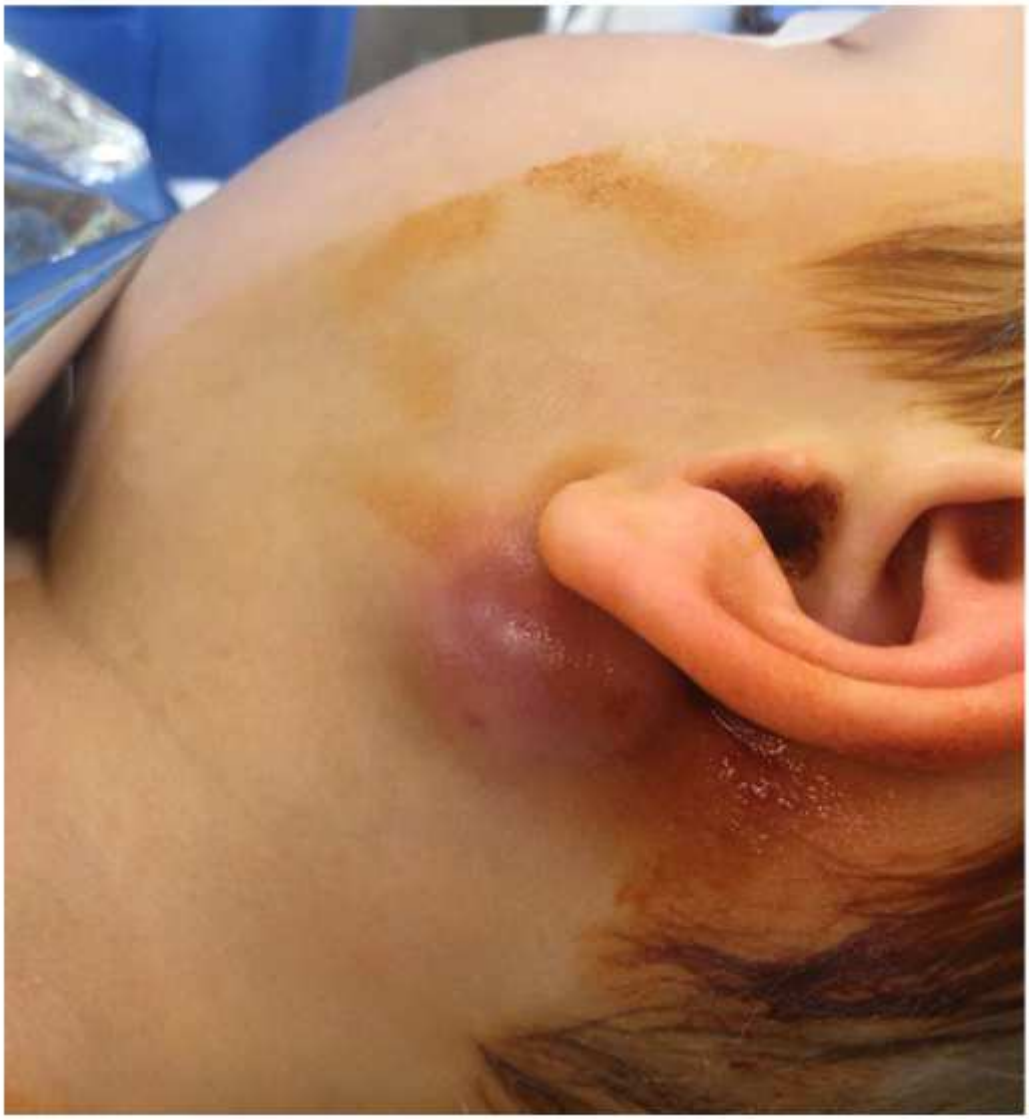

Figure 1

Left parodid swelling before surgery

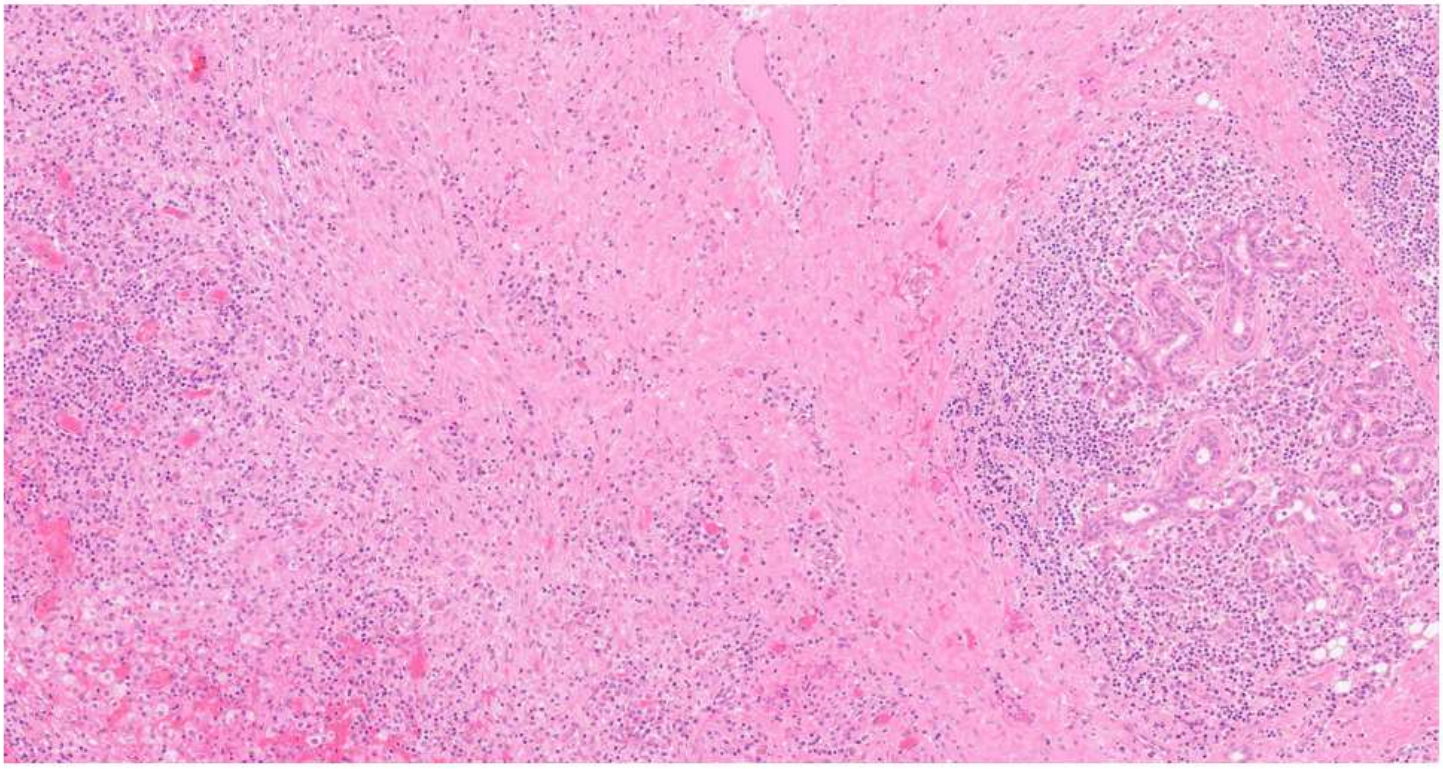

Figure 2

Interlobular fibrosis with dense lymphoplasmacellular infiltrate (hematoxylin and eosin, 10x magnification)

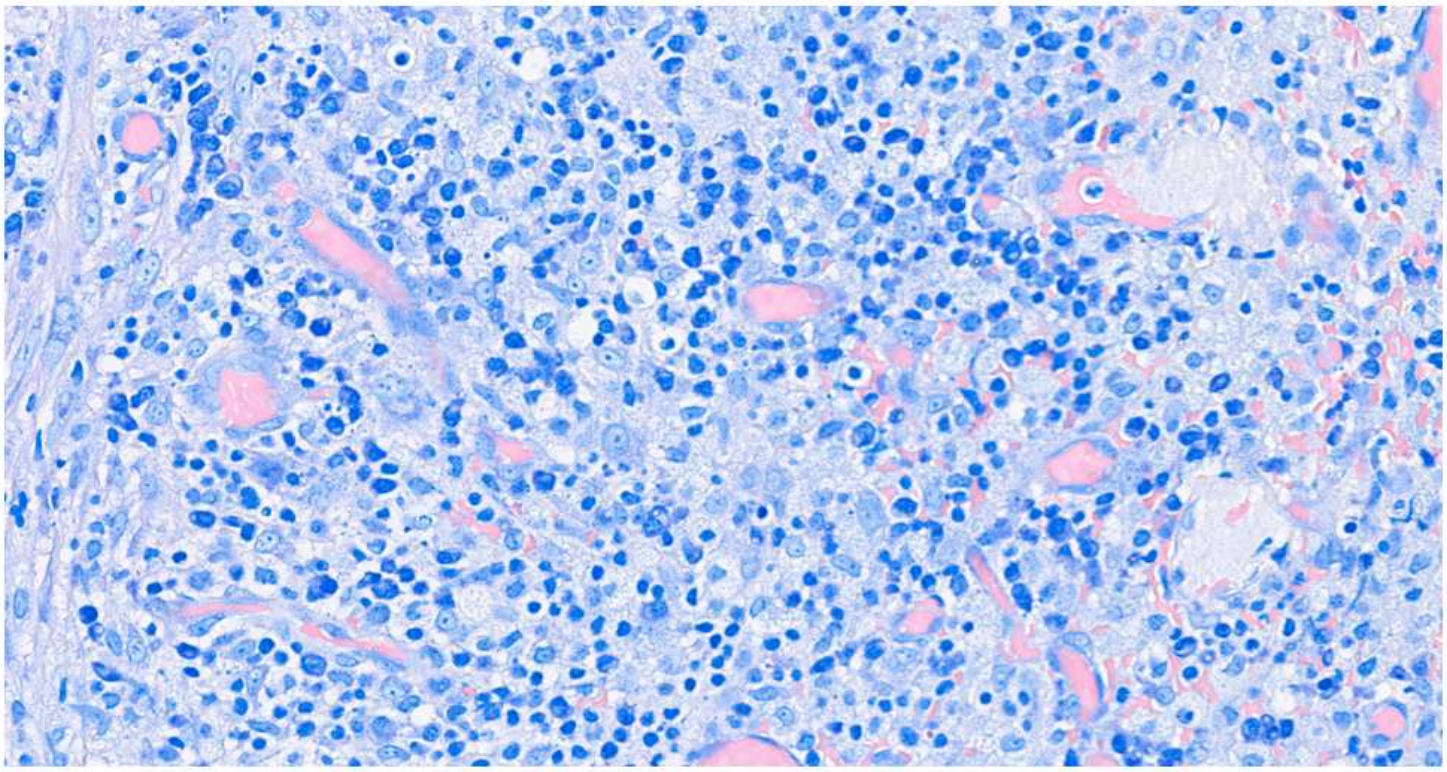

Figure 3

High number of plasma cells (Giemsa, 40x magnification)

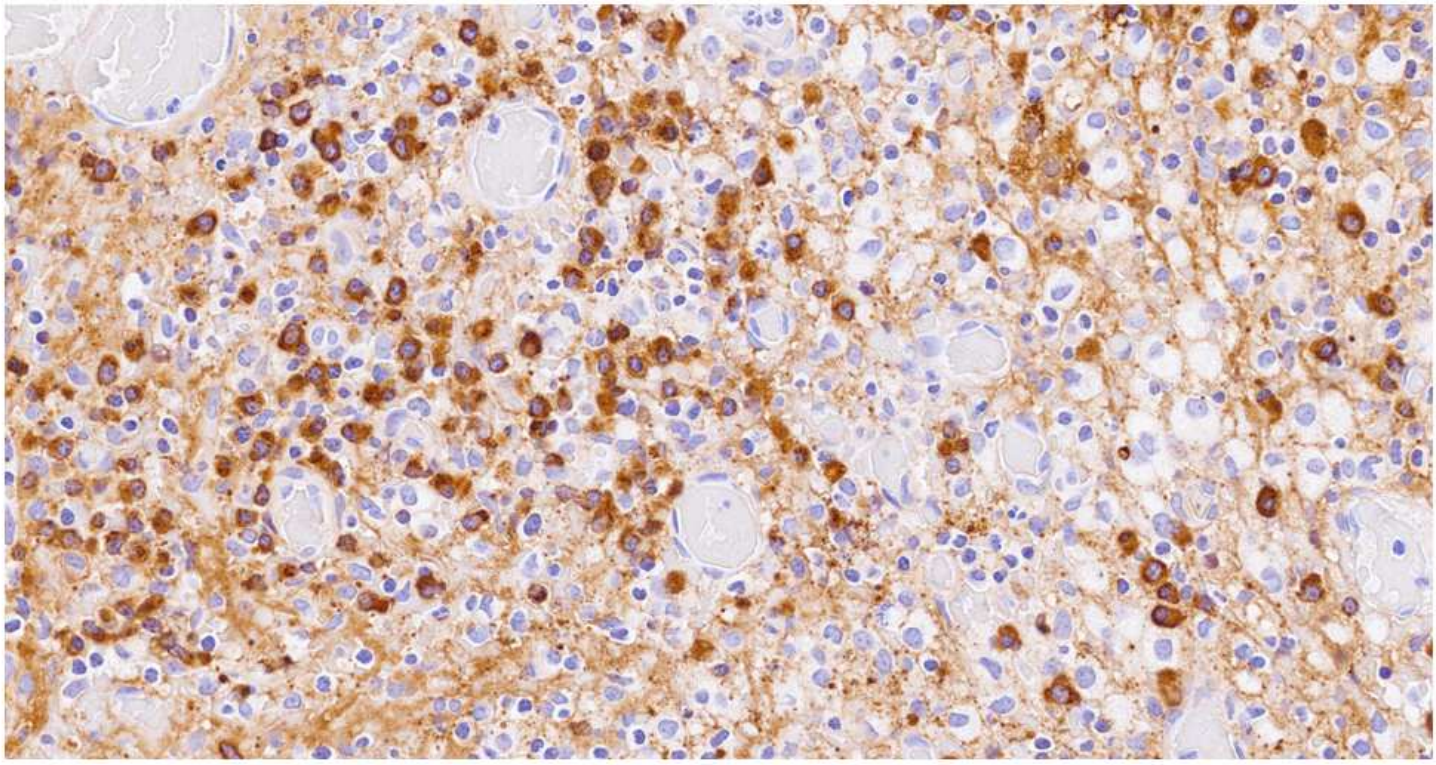

Figure 4

Plasma cell with strong cytoplasmatic expression for IgG (IgG immunohistochemistry, 40x magnification)

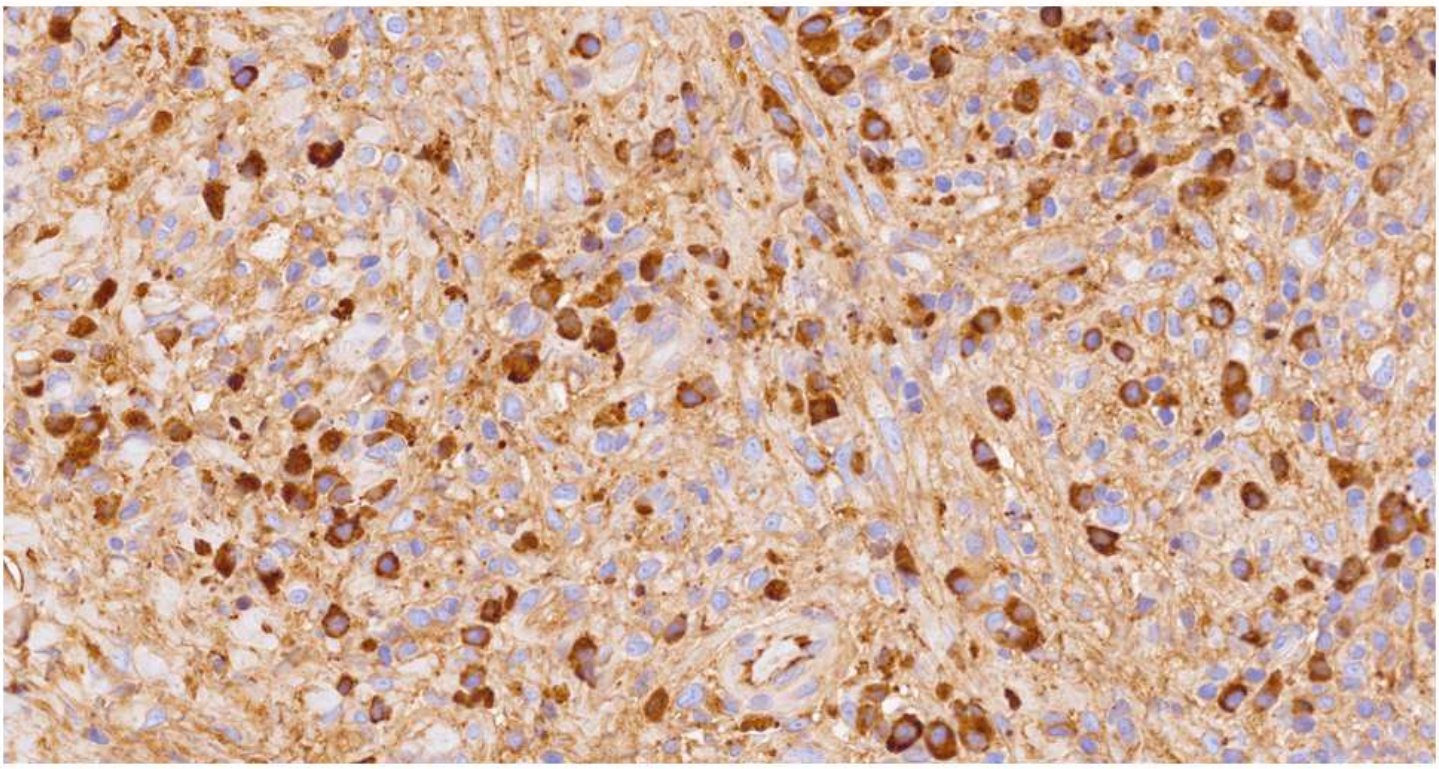

Figure 5

Plasma cell with strong cytoplasmatic expression for IgG4 (IgG4 immunohistochemistry, 40x magnification)