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SEVERE HEADACHE IN PRIMARY SJÖGREN'S SYNDROME RESPONDED TO RITUXIMAB

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ABSTRACT

Introduction: Primary Sjögren syndrome (pSS) is an immune systemic disease, that may affect the central nervous system. A severe headache unresponsive to treatment is the headache which is persistently nonresponsive to narcotic analgesics.
Case presentation: A 48-year-old woman with a 10-year history of pSS was seen in January 2021, complaining of a headache one week previously. The headache was characterised by a dull persistent pressing intensity and was not responding to paracetamol, NSAIDs or codeine. She had no previous history, nor family history. Physical examination revealed bilateral parotid glands enlargement. Laboratory tests showed anaemia, and elevated levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), with positive anti-La and anti-Ro antibodies. She was given topical treatment and different doses of Predlone, in addition to methotrexate10 mg/week. She had received three pulses of methylprednisolone and was started on azathioprine with a mild response to the headaches, so she received two initial IV doses of rituximab 375 mg/m^2, then every 2 weeks, with a clinical and laboratory response. Two years later, she had no headache.
Discussion: Headache that may presented in pSS are tension headaches, migraines and cluster headaches. The therapy is disease-modifying antirheumatic drugs, hydroxychloroquine, glucocorticoids and biotherapeutics. Rituximab is used in the treatment of some patients with pSS, especially where it can affect systemic symptoms.
Conclusion: Rituximab treatment may be an option for severe headache in patients with pSS. The mechanism is unknown but may be due to depletion of brain auto-reactive B cells. Further research is needed.

KEYWORDS

Rituximab, headache, primary Sjögren's syndrome

LEARNING POINTS

- An unresponsive headache in a patient with primary Sjögren's syndrome treated with tryptophan, opioids and NSAIDs responded successfully to B-cell depletion with rituximab.
- We hypothesise that brain-autoreactive B cells were involved in the pathogenesis of the headache.

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INTRODUCTION

Primary Sjögren's syndrome is an immune systemic disease, involving many organs including the central nervous system[1]. Headaches are common in Sjögren's, estimated to occur in 50% to 75% of patients[2].

Primary headache disorders such as migraine, tension-type and cluster headache may be found in primary Sjögren's syndrome. In addition, a history of pre-existing or a family history of headache is helpful for the diagnosis[3].

Some research comparing Sjögren's patients with healthy controls show that tension-type headaches and migraine headaches, the most frequent headache subtypes found in Sjögren's, are more common in Sjögren's patients than in the normal population[4]. Other data demonstrate headaches are more severe in those with Sjögren's than in those of the normal population with depression as a significant influence on headache severity[3,5]. Sjögren's patients may also develop a rare and particularly severe type of headache due to aseptic meningitis[5].

In general, treatment for routine headaches is the same in those with Sjögren's as it is for anyone else including acetaminophen or ibuprofen. Treatment for aseptic meningitis may also involve glucocorticoids such as prednisone[3,4]. A severe headache unresponsive to treatment is the headache which is persistently nonresponsive to narcotic analgesics[3]. We report a case of an unresponsive headache successfully treated with rituximab in primary Sjögren's syndrome.

CASE PRESENTATION

A 48-year-old female with a 10-year history of pSS was seen in the out-patient clinic of Modern Medical Hospital, Damascus, Syria, in January 2021, complaining of an intense and disabling headache one week previously. The headache was characterised by a dull persistent pressing intensity and not responding to paracetamol, NSAIDs or codeine. On a visual analogue scale 0–10, she rated the intensity as 10; she was on 10 mg/week methotrexate. The diagnosis was based on the American College of Rheumatology, and the European Alliance of Associations for Rheumatism (ACR/EULAR) criteria[6]. She had no previous history of headache, nor family history of cluster headache or migraine. Physical examination revealed bilateral glands enlargement *(Fig. 1,2)*. The remain examination, including the neurological examination, was within normal limits. No signs were found concerning Raynaud phenomenon. Laboratory tests showed: haemoglobin 10.1 mg/dl (11.7–15.3), IgG 12.3 g/L (5.4–18.2), ESR 83 mm/hr and CRP 11.2 mg/dl (<6). The viral serology including HIV and hepatitis B and C virus, human parvovirus B19 IgM, Epstein-Barr virus IgM, Mycoplasma DNA, rapid influenza antigen and VDRL were also negative. Anti-streptolysin O antibody and anti-streptokinase antibody were negative. Borrelia IgG and IgM, and Treponema pallidum haemagglutination tests were negative. Immune profile tests showed anti-La 11.3 units/ml (n;<7 units/ml), and anti-Ro 17.1 units/ml (n;<7 units/ml).

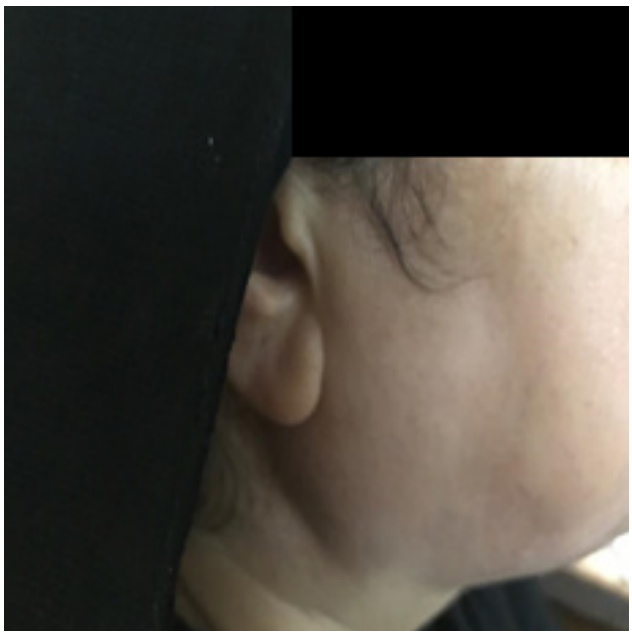

Figure 1. Right parotid enlargement

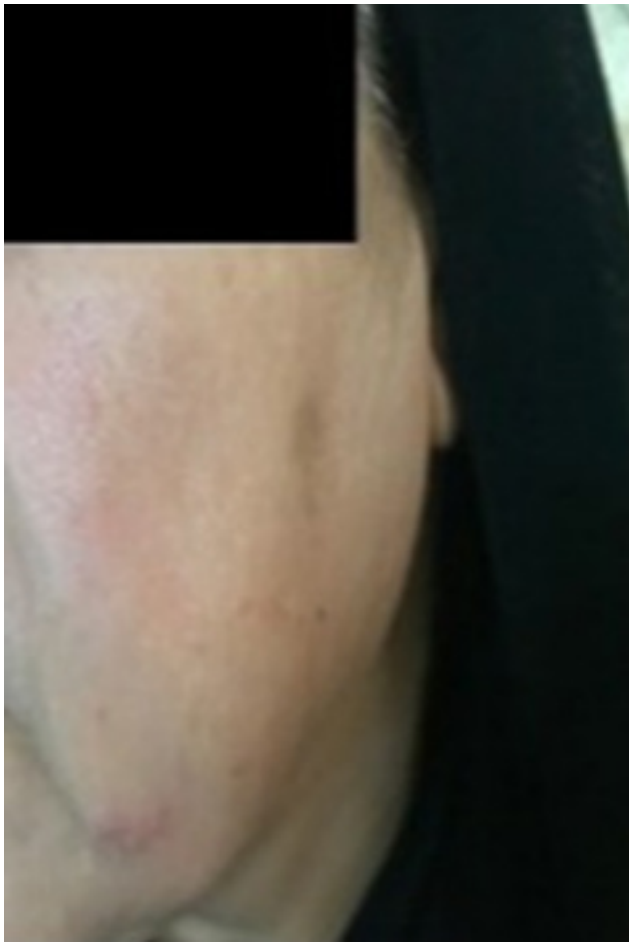

Figure 2. Left parotid enlargement

Cerebral spinal fluid analysis was normal. Cerebral MRI and intracranial arterial and venous MRI angiography were normal.

The patient was treated with topical treatment for dry eye and dry mouth, and different doses of Predlone, ranging from 5–60 mg/day, according to the disease activity.

She had received three pulses of methylprednisolone 1000

mg and was started on azathioprine 150 mg (2 mg/kg/day) with a mild response to the headaches. Because of persistent disease activity, she received two initial IV doses of rituximab 375 mg/m^2 every 2 weeks, with a clinical response, as her fatigue and headache were decreased. The ESR and CRP return to normal. At 6 months, disease activity decreased and the headaches also decreased, still persist but low intensity, and for that methotrexate was added at dose of 10 mg/week. Two years later on 10 mg/week methotrexate, she was in remission and had no headache.

DISCUSSION

Primary Sjögren's syndrome (pSS) is a systemic disease involving many systems including CNS, with a predominance of females and a middle-aged population[1]. Our patient is a female aged 48 years and was diagnosed at the age of 38 years.

Headache is a neurological manifestation of many immunological and autoimmune conditions[6]. Headaches are common in Sjögren's, estimated to occur in 50% to 75% of patients[2]. Headache types that may be presented in pSS are tension headaches, migraines and cluster headaches. Immuno-mediated disease activity without clinical presentations or laboratory markers may trigger a vascular headache such as migraine in these patients[2,5,7,8].

Ectopic germinal centres consisting of follicular plasma cells, dendritic cells, and B and T cells, which may develop in pSS, seem to reveal a high disease activity and an increased tendency for transforming to B-cell lymphoma[2,5,8].

The patient could have brain resident immune cells, which are not evident on an MRI or in the cerebrospinal fluid. These B cells are not depleted by rituximab as this drug cannot pass the blood-barrier of the brain. This could affect or disturb the cerebral homeostasis, thus trigging and maintaining the migraine headaches[9]. A possible link between migraine and Raynaud's phenomenon has been suggested[10].

The traditional therapy is disease-modifying antirheumatic drugs such as methotrexate, mycophenolate mofetil, azathioprine and cyclophosphamide, or hydroxychloroquine and glucocorticoids, while novel biotherapeutic approaches targeting Th17 cell- and B-cell-related signalling pathways and molecular events has drawn increasing attention[11].

Rituximab is a chimeric antibody that binds to the CD20 antigen with an expression on B-cell progenitors, facilitating their activation, proliferation and differentiation. It is used in the treatment of some patients with pSS, especially where it can affect systemic symptoms[12,13]. Rituximab restores the morphology of ductal epithelium in salivary glands; the beneficial clinical effects of rituximab vary between studies. Patients with systemic involvement may benefit most from treatment[14]. Rituximab has been useful in Sjögren's-related neuropathy, although it remains unclear whether it is effective in small fibre neuropathy[15,16].

In general, treatment for routine headaches is the same in those with Sjögren's as it is for anyone else, including the use of acetaminophen or ibuprofen. Treatment for aseptic meningitis may also involve glucocorticoids such as prednisone[3,4].

In this case, the failure to respond to all other treatments except rituximab strongly suggests that it was related to pSS. The most frequent side effects of rituximab are infusion-related reactions, infections, body aches and hair loss[11,16]. There were no side effects or complications of rituximab found in this case.

CONCLUSION

Headache is frequently presented as a systemic manifestation in pSS. Rituximab treatment may be an option for severe headache in patients with pSS and other autoimmune diseases. The mechanism is unknown but may be due to depletion of brain auto-reactive B cells. Further research is needed concerning a headache in pSS patients to determine optimal treatment strategies.

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