

## **A Case of Morbihan Disease Refractory to Medical Treatment**

**Geronazzo G<sup>1</sup>, Nicola S<sup>1</sup>, Lo Sardo L.<sup>1</sup>, Fornero M.<sup>2</sup>, Ruka E.<sup>3</sup>, Brussino L.<sup>1</sup>, Rolla G.<sup>1</sup>**

<sup>1</sup>Department of Medical Science, University of Turin, Italy

<sup>2</sup>Allergy and Immunology Unit, Mauriziano Hospital, Turin, Italy

<sup>3</sup>Plastic Surgery, Mauriziano Hospital, Turin, Italy

\*Corresponding author: Fornero Monica, Allergy and Immunology Unit, Mauriziano Hospital, Turin, Italy. Email: fornero.monica@gmail.com

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### **Case Report**

In September 2018 we examined a 42 years old man complaining about periorbital edema, referred as persistent for several years but exacerbated in the months before the outpatient visit. The patient also had a papulo-pustular rosacea (Figure 1).

Routine blood tests were normal, except for Antinuclear Antibody positivity (medium titer ANA with fine granular pattern / AC-2) and anti-DSF70 (dense fine speckled) antibodies. The patient was already treated with corticosteroids, hydroxychloroquine and cyclosporine, without any effectiveness on clinical signs.

As a first step, we prescribed Doxycycline low dose (40 mg) and Metronidazole cream 0.75% for the treatment of the underlying rosacea and we recommended daily photoprotection (SPF 50+).

Two months later, the patient did not show any improvement, thus persisting a massive periorbital oedema (greater on the right side) which involved eyelids and malar region and was associated with a mild skin erythema: a diagnosis of Morbihan disease was made.

Following the current literature, we started a treatment with Isotretinoin 0.3 mg/Kg (25 mg) and Deflazacort 30 mg. Four weeks later, not only were erythema and orbital oedema still present but, the patient also reported irritability and lip xerosis. We decided to tapering Deflazacort without modifying Isotretinoin dosing schedule.

As no benefit was observed after three more weeks, and being blood tests (complete blood count, erythrocyte sedimentation rate (ESR), creatinine, glycaemia, liver function tests) normal, we reduced up to withdrawal Deflazacort and Isotretinoin. Doxycycline 200 mg daily was then started.

On 21st February 2019, the patient reported a complete resolution of lip dryness, but he complained a significant worsening in periorbital oedema, which did not allow him opening the eyes. We prescribed Deflazacort 15 mg and Isotretinoin 10 mg

again, reducing Doxycycline up to 100 mg/day.

At the end of March, oedema was limited to the right periorbital region. We recommended therefore to maintain the current dose of Doxycycline (100 mg) and Isotretinoin (10 mg) and to reduce Deflazacort to 7.5 mg/day, even considering the relapsing in nervousness.

In May, the patient was evaluated by the plastic surgeon, who performed a local infiltration of triamcinolone in upper and lower eyelids. He also performed a periorbital incision with subsequent subcutaneous detachment of thickened dermis and muscle and removal of the exceeding deep subcutaneous and fibrous connective tissue, resulting in satisfactory aesthetic and functional outcomes with improvement of visual field (Figure 2). During the surgical procedure multiple biopsies were performed: the histological examination showed a slight perivascular inflammation in the connective tissue with lymphoplasmacytic inflammation and multiple vasal ectasias in the skin, but rare mast cells.

### **Discussion**

Morbihan disease is a lymphangitic complication of Rosacea, characterized by solid and persistent oedema of the upper face [1], with no spontaneous remission [2]. It is often associated with frequent episodes of flushing, fixed erythema, spider veins, papules and pustules [3]. In most cases, it has a bilateral presentation, but there are some case reports about unilateral Morbihan Syndrome [4,5]. The pathogenesis of this disease is still unknown, but it is probably linked to recurrent episodes of vasodilation and inflammation. These result in damage, remodeling and formation of epithelioid granulomas and lymphohistiocytic infiltrates around lymphatic vessels, with consequent drainage alteration [1,6,7]. The disease more commonly appears in the third and fourth decades, with greater incidence in women [2].

Symptoms are usually minimal, but, when eyelids involvement is present (as in our patient was), aesthetic alterations of facial features and visual field limitations can occur [8,9], with a considerable worsening patients' quality of life.

A suspicion of Morbihan Syndrome should arise in patients



Figure 1: Patient's first presentation



Figure 2: Patient before and after surgery

with a chronic, refractory oedema, without any specific abnormalities to lab tests nor histological examinations [10-12]; a few patients show infiltration consistent with a mast cells inflammation [6,13]. Morbihan Syndrome is a diagnosis of exclusion, so it is mandatory to consider any other differential diagnosis, such as oro-facial granulomatosis, sarcoidosis, Hansen's disease, Systemic Lupus Erythematosus, cutaneous leishmania, foreign body granulomatosis, facial granuloma, superior vena cava syndrome, Buschke's scleredema, pseudolymphoma, Melkersson-Rosenthal's syndrome, dermatomyositis, chronic actinic dermatitis, chronic contact dermatitis, angioedema or thyroid disease and drug reactions (barbiturates, chlorpromazine, diltiazem and isotretinoin) [2,3,6,13].

In our patient, the presence of rosacea and the typical presentation drove us to the suspicion of t Morbihan disease. Furthermore, anti-DSF70 antibodies in a patient with ANA-positivity made the presence of immune-rheumatologic diseases unlikely [14].

The therapy we chose was supported by the studies published in literature [12]:

- Treatment of basic rosacea: since our patient had a papulo-pustular rosacea, we decided to start therapy with a topical anti-inflammatory agent (Metronidazole cream 0.75%). It works altering neutrophil chemotaxis and inactivating ROS, in order to reduce erythema, papules and pustules. We also added an oral antibiotic at reduced doses (Doxycycline 40 mg) [15];
- Isotretinoin: Isotretinoin at a dose of 10-80 mg for 3-6 months has proved to be effective in most studies carried out on patients with massive mast cells infiltration [2,8,9], leading to disease-free intervals of about 9 months [6,16]. Also a long term therapy with ultra-low dose of Isotretinoin (10 mg) and Desloratadine 5 mg given for 12-16 month seems to be



Figure 3: Patient 3 months after surgery

effective [17]. However, in 15-20% of patients this drug is ineffective: in these cases, the disease course is uncertain, with possible chronic evolution or exacerbations [7];

- Deflazacort: corticosteroids are used thanks to their anti-inflammatory power that inhibits mast cells activation, migration, proliferation and cytokine production and neutrophils recruitment [6], but steroid use in monotherapy must be carefully evaluated, as it could be related to the disease recurrence or progression, since it does not act on pathogenetic mechanisms at its base [1]. Steroids intralesional administration appears effective, safe and minimally invasive and could have more satisfactory results, as the effects would not be impaired by persistent lymphedema and perivascular inflammation. For this reason, our patient was referred to the plastic surgery department, where, in addition to performing a biopsy, he was treated with to local injection of Triamcinolone;

- Doxycycline: the use of tetracyclines is emerging in patients with Morbihan disease, thanks to the ability of the drug in inhibition of cytokines production (in particular, antimicrobial peptide LL37 and metalloproteases that have vasodilatory effects) [16] by mast cells [8,12]; different from the previous therapy, however, the duration of antibiotic treatment relates with the degree of response obtained [1]. In particular, Doxycycline given at a reduced dose (40 mg/day in the prolonged release formulation) for 4-12 months seems to be effective in inducing complete remission, as it improves cellular metabolism in damaged tissues and reduces the damage of the extracellular dermal matrix, with antiproliferative effect on fibroblast activity; furthermore, at these doses, it is not associated with side effects or onset of resistance [11,16];

- Blepharoplasty: when medical therapy results inadequate, surgical therapy could be a choice; however, after this procedure, disease outcomes or relapses cannot be ruled out [10].

Other therapies that have been studied: facial draining massage [18], blepharoplasty with CO<sub>2</sub>-laser [2], Minocycline (in countries where Isotretinoin is not on the market) [8,19], IFN-gamma injection [3], Thalidomide (with poor results) [3,9], Tripterygium wifordii (extracted from a traditional Chinese herb and having anti-inflammatory and immunosuppressive properties) [19] and Omalizumab at initial dose of 450 mg and consecutive maintenance doses of 300 mg every 4-6 week for 2 months [20].

Despite several available drugs, capable of acting on factors

apparently triggering the phenomenon, we must remember that they may be ineffective in case of excessive accumulation of fluids in the interstice and the reduced perfusion of the fibrous and collagenous thickness, which prevent the correct drugs distribution in involved areas [10]. Moreover, in patients presenting with a low mast cell infiltrate those drugs would have fewer targets to act on.

Currently, combined therapy with antibiotics and steroids seems to be the most commonly used, but it is necessary to consider adverse effects [1].

## Conclusions

Despite in our patient the diagnosis was facilitated by a typical clinical presentation, this case showed an inadequate response to the standard therapy, requiring the concomitant use of Isotretinoin, corticosteroids and oral tetracyclines for a prolonged time (over 5 months) with only partial benefit. This was probably also due to the lack in mast cell massive infiltration. Consequently, surgical therapy, combined with local infiltration of Triamcinolone, seemed to be the only treatment able to improve patient's quality of life, even if we are aware that it does not ensure definitive results.

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