

# Remission and relapse in granulomatosis with polyangiitis in a young woman

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## ABSTRACT

Granulomatosis with polyangiitis (GPA) is a rare disorder characterized by inflammation of small and medium-sized blood vessels (vasculitis) that results in damage to various organ systems of the body, most often the respiratory tract and kidneys. The relapse rate rises from about 20% at 12 months to about 60% at 5 years. The combination of glucocorticoids and cyclophosphamide remains the standard therapy for patients with generalised GPA. Nevertheless, some patients do not respond satisfactorily to this treatment. Here we present a 32 year-old female with relapsing GPA successfully treated with methotrexate for ear, nose and throat (ENT) manifestation.

**Keywords:** rheumatoid arthritis, autoantibody, autoimmunity, relatives

## INTRODUCTION

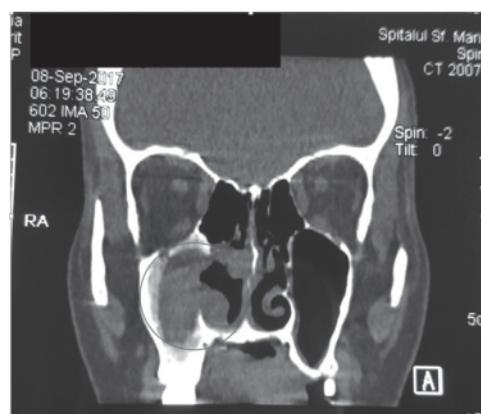
Granulomatosis with polyangiitis (GPA) is a rare disorder characterized by inflammation of small and medium-sized blood vessels (vasculitis) that results in damage to various organ systems of the body, most often the respiratory tract and kidneys (1). The relapse rate rises from about 20% at 12 months to about 60% at 5 years. The combination of glucocorticoids and cyclophosphamide remains the standard therapy for patients with generalised GPA. Nevertheless, some patients do not respond satisfactorily to this treatment (2).

## CASE REPORT

We present a rare case of a patient presenting to us in July 2017 with recurrent episodes of headache, chronic nasal obstruction and anterior rhinorrhea. She presented to a specific dental clinic where she receives specialized treatment. After the treatment with painkillers, the symptomatology did not improve, which is why an ENT consultation is performed that confirms

bilateral maxillary rhinitis. A drainage of the maxillary sinus was made and systemic antibiotic therapy and corticosteroid was recommended with short-term improvement of symptoms.

A native CT sinuses was performed on this patient and founded chronic inflammatory process in the maxillary sinuses on the right side, with extension to the right nasal fossa (Fig. 1).



**FIGURE 1.** Chronic inflammatory process in the maxillary sinuses on the right side

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In June 2017, she presented to another ENT department where she performed an endoscopic maxillary anrostomy, antral lavage and right maxillary sinus drainage. Also, multiple rhinosinusitis mucosal biopsies were made at this time.

Histological sections showed inflammatory lympho-plasmocyte infiltrate, multinucleated giant cells, small vessels with focal areas of fibrinoid necrosis, perivascular chronic inflammatory infiltrate. Immunohistochemical staining showed large atypical cells to be CD20 positive B-cells.

In July 2017 the patient was admitted to our department for the first time. The physical examination revealed “saddle-nose deformity” (Fig. 2) and crusts in the nose.



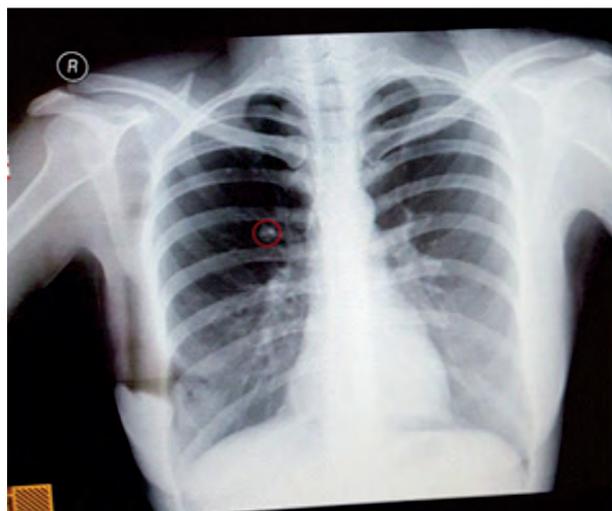
**FIGURE 2.** Saddle nose deformity”

Laboratory tests were significant for normocytic normochromic anaemia (haemoglobin 10.2 g/dl), mild leucocytosis (white blood cells 11.3/l), thrombocytosis (PLT 437 G/l), erythrocyte sedimentation rate (ESR) 42 mm/h (normal range 0-30 mm/h) and C-reactive protein (CRP) 37 mg/dl (normal range 0-5). Urine test and creatinine level were normal. Blood test revealed positivity for cANCA antibodies 13 U/ml (positive > 5 U/ml). Pharyngeal and nasal cultures were positive for *Staphylococcus aureus*.

The chest radiograph showed diffuse interstitial lung disease (Fig. 3) interpreted by pulmonologist in the context of the underlying disease.

Based on clinical presentation with ENT involvement and presence of cANCA antibodies, the granulomatosis with polyangiitis (GPA) was recognized.

Its' clinical activity was assessed using a disease-specific activity index the Birmingham Vasculitis Activity Score modification for GPA (BVAS = 6 points) (3). According to European Vasculitis Study Group (EUVAS) recommendations in 2016 for induction (4), the patient was treated with glucocorticoid pulses (methylprednisolone 3 × 500 mg i.v.) and pulses of cyclophosphamide (CYC) in dose 15 mg/kg/infusion with frequency of administration every 4 weeks for 6 months. Prophylaxis against infection with *Pneumocystis jirovecii* with trimethoprim/sulfamethoxazole was also administrated.



**FIGURE 3.** Diffuse interstitial lung disease

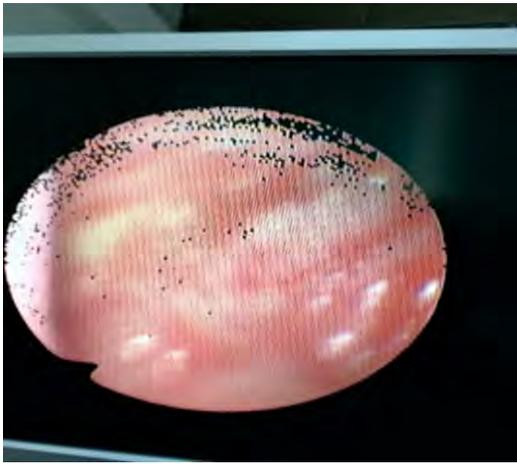
After 6 months of treatment, in march 2018, the crusts in the nose have healed, cANCA titers decreased (cANCA 1.8 U/ml) and inflammatory markers improved.

For inducing remission, according also to EUVAS (5), the patient received treatment with azathioprine (100 mg/day) and low-dose steroids (prednisone 10 mg/day).

Since april 2018 until June 2019, the patient got regular check-ups with a well response to the treatment.

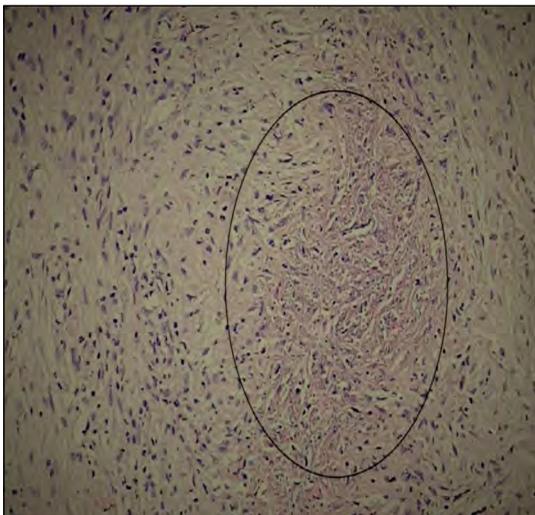
In June 2019, the patient presented again with headaches on the left side and anterior rhinorrhea.

Laboratory tests were significant for CRP 55mg/l, cANCA increased. Nasal cultures were repeated in case of any symptoms of infection, but were negative. There were no laboratory symptoms of renal involvement (creatinine concentration and urine tests were normal). Anterior rhinoscopy showed destruction of the left sinus wall (Fig. 4). Mucosal biopsies were also taken.

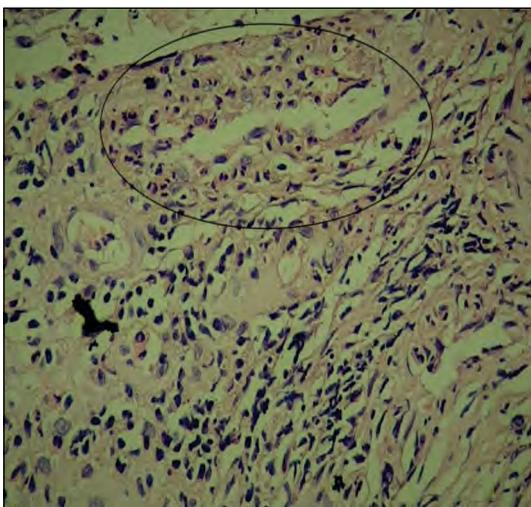


**FIGURE 4.** Destruction left sinus wall

Histopathological examination showed acellular amorphous areas containing karyorrhectic debris (tissue necrosis) and an associated inflammation, composed largely of neutrophils, extending into the vascular wall (vasculitis) (Fig. 5, 6).



**FIGURE 5.** Vascular necrosis



**FIGURE 6.** Vasculitis

Repeated native CT sinuses revealed, this time, collection of left ethmoidal cells, bilateral maxillary and ethmoidal sinusitis (Fig. 7).



**FIGURE 7.** Collection of left ethmoidal cells, destruction of the maxillary sinus bone structures

At this moment, the patient was considered to have a relapse with clinical activity BVAS = 8 points. Considering the patient's age and the desire to have another child, it was decided to change the immunosuppressive treatment to methotrexate 25mg/week and folic acid to reduce side effects. Also, glucocorticoid pulses (methylprednisolone 3 × 500 mg i.v.) and steroid nasal irrigation was associated.

During assessment 6 months after initiation of methotrexate, the clinical remission was noted (BVAS = 0 points), the cANCA titres decreased significantly (3.4 U/ml), laboratory tests were within normal ranges, except mild leukocytosis due to the long-term pattern of prednisone-induced.

The physical examination revealed no headache and no anterior rhinorrhea (Fig. 8). An easy cushingoid appearance was noted due to prolonged period treatment with glucocorticoids.

The patient was treated with methotrexate (25 mg/week) and decreasing glucocorticoids to maintenance the remission.

## DISCUSSION

Granulomatosis with polyangiitis is a chronic relapsing disease. Cyclophosphamide and glucocorticoids have been the standard of remission induction therapy for generalized GPA for many years. CYC induction regimens are effective in 70-90% of pa-



**FIGURE 8.** Physical examination

tients, but a considerable number of patients are resistant to standard treatment.

The presented patient had localized disease, only ENT involvement. It is worth highlighting the differences in recommendations regarding to this aspect. The 2009 recommendations suggested that methotrexate use was reasonable for those patients. However, the new recommendations have differentiated even localised disease into that with and without cartilage and bony involvement, the argument being that destruction of nasal tissues is an organ threatening manifestation and the treatment is as above (5).

The risk of serious bacterial infectious after an immunosuppressive therapy, especially used in severe and refractory cases of systemic autoimmune

diseases, is well known. There is a strong possibility that the initial adverse effects of remission induction are related to glucocorticoid treatment.

## CONCLUSIONS

This case emphasises that relapsing GPA was successfully treated with methotrexate for ear, nose and throat manifestation in this patient. In such cases intensive induction immunosuppression is required. Our case report highlights that localised GPA is not necessarily indolent and that methotrexate may be adequate treatment for localised disease. Finally, such cases should be managed by a multi-disciplinary team in a tertiary referral centre.

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