Sinusogenes orbital complication as the first symptom of refractory granulomatosis with polyangiitis and the use of rituximab in treatment. A case report

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ABSTRACT

Granulomatosis with polyangiitis (GPA) is a rare disease involving multiple organs and systems, characterized by necrotizing inflammation of small and medium-sized vessels and formation of granulomas. There are several forms of the disease. In the generalized form (including severe one), cyclophosphamide in combination with steroids is usually used. There are also cases of a particularly severe and refractory course of the disease, which do not respond to the standard treatment. In such cases some other methods of treatment are recommended, including biological agents such as rituximab - anti-CD20 monoclonal antibody. We described a case of a 17-year-old patient with refractory GPA, resistant to standard remission induction therapy. In case of this patient, advanced lesions were mainly localized in the lungs, sinuses and middle ear. The disease progressed despite standard therapy. Therefore, it was decided to use an alternative treatment with a biological agent – rituximab. In the assessment after therapy we observed a significant clinical recovery as well as the improvement in laboratory tests, pulmonary function tests and radiological imaging. Within six months after the administration of rituximab, progression of the disease was not observed, which was evidenced in radiological imaging and pulmonary function tests. The case illustrates how biological agents, including rituximab, are extending the therapeutic options for patients with GPA, especially with severe forms of the disease.

Key words: granulomatosis with polyangiitis, refractory GPA, rituximab

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INTRODUCTION

Granulomatosis with polyangiitis (GPA) is a rare disease which usually involves numerous organs such as the upper and lower respiratory tracts, as well as the kidneys. A limited variant of the disease, which involves the nose, ears and larynx is also described. The feature characteristic for this disease is the presence of antineutrophil cytoplasmic antiboidies of the cytoplasmic type of lighting in the indirect immunofluorescence (c-ANCA), reacting with proteinase 3 in the immunosorbent assay (ELISA). Their prevalence in patients with GPA is estimated to be 80-90%, but their absence does not exclude the diagnosis of the disease [1].

ANCA are assigned a pathogenetic role in GPA. Their titre is often correlated with disease activity. The incidence of GPA in the adult population is reported as 3 to 14 cases/million/year [2].

However, there are only a few papers describing the occurrence of GPA in children. One of the first announcements came from Sweden.

Stegmayr et al. [3] describe the incidence of GPA in young adults (18-30 years old). Their findings showed large differences compared to the adult population: 0.5 cases/million per year. However, current publications have confirmed the same prevalence between these two groups [4].

Moreover, GPA is the most common chronic primary systemic vasculitis in childhood, and affects between 0.03 and 3.2 children per 100,000 per year. There are, however, differences in the clinical course of GPA between adults and children. In the latter, nasal deformation as well as subglottic stenosis are present more often.

The European League Against Rheumatism, Pediatric Rheumatology International Trials Organization, Pediatric Rheumatology European Society (EULAR, PRINTO, PRES) proposed classification criteria for childhood GPA [5,6].

The new criteria include: sinus inflammation and subglottic, tracheal, or endobronchial stenosis. Regarding the new classification, the upper airway involvement includes recurrent epistaxis, nasal crusting, nasal septum perforation, saddle-nose deformity, and chronic or recurrent sinus inflammation [5,6].

In this paper we present a 17-year-old patient with a severe form of GPA, who experienced disease progression despite conventional treatment, and in whom the use of rituximab allowed to stop the progression of the disease and to obtain clinical improvement.

Case presentation

A 17-year-old man, K.P., was admitted to the Department of Otolaryngology and Laryngological Oncology in Poznan, Poland on 24th March 2011 due to the exacerbation of sinusitis. The patient was initially treated at a municipal hospital, where he had received an antibiotic therapy without effects. On the day of admission he complained of severe headaches, but was verbally coherent and had no fever. Basic blood tests detected increased levels of leukocytes and a growth in inflammatory parameters. The chest X-ray was normal. A check-up CT of the paranasal sinuses revealed right-sided sinusitis (Fig. 1).

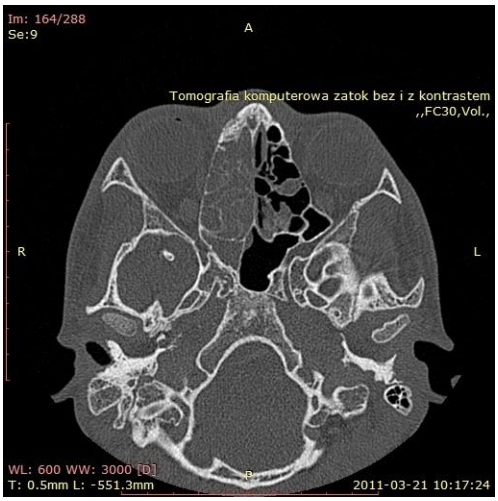

Fig. 1. Computed tomography shows right-sided sinusitis with involvement of anterior and posterior ethmoid and sphenoid sinuses (arrows)

Besides, the patient's right eyelid had swollen. Magnetic resonance imaging of the head excluded intracranial complications. Considering the above clinical picture and no clinical improvement after a traditional treatment, a functional endoscopic sinus surgery was carried out. Material was sent for histological examination, which revealed chronic rhinitis with lymphocytic infiltration. On the 7th day the patient was discharged in a good general condition.

11 days later the patient again developed swelling of the right eyelid and thickening of the right angle of the eye. CT found inflammatory changes in all sinuses and of the right lacrimal gland. The picture resembled the formation of an abscess. Based on the presented clinical picture, a decision was made to perform a sinus surgery and to re-examine the right eye socket. On 12th April 2011 bilateral endoscopic surgery was carried out.

After opening the right eye socket no pus was found inside. A wide range of antibiotics was ordered by a consultant bacteriologist. Initially, inflammatory parameters decreased. On the third day after the operation the patient's temperature rose to above 39 degrees. In the following days the patient developed a gradually increasing cough and difficulty in breathing, accompanied by chest pain. Chest CT revealed numerous bilateral round

shadows, ranging from 3 mm to 32 mm in size. A number of swabs was taken from the surgical site, and a growth of Staphylococcus aureus was repeatedly reported. Despite the fact that a broad spectrum antibiotic therapy was continued, parameters did not improve. In the meantime, tests were ordered to measure the titre of ANA and ANCA antibodies. The results of these tests showed a very high titre of cANCA (139 RU/ml), which allowed to establish the diagnosis of granulomatosis with polyangiitis (GPA).

Due to the clinical predominance of pulmonary changes, the patient was referred for further treatment to the Department of Pulmonology of the University of Medical Sciences in Poznan, where he was first admitted in May 2011.

On admission to the Department of Pulmonology the patient complained of tooth pain and severe facial pain, localized mainly in the forehead. In addition, he complained of a productive cough with expectoration of purulent sputum, as well as poor exercise tolerance and general weakness.

High-resolution computed tomography of the chest showed multiple nodules up to 10 mm in diameter, located in the upper-middle parts of both lungs and near pleura, and several nodular changes with decay cavities up to 30 mm in diameter, accompanied by peribronchial infiltrates. Bronchofiberoscopy revealed pointed swollen bronchial mucosa with many papular changes throughout the whole bronchial tree. Mucosal specimens were taken for histopathological examination and revealed bronchial mucosa with sanguineous and purulent exsudate; histiocytes, fibroblasts and isolated multinucleated giant cells were present among the inflammatory cells. Necrosis or infiltration of eosinophils were not seen, although total microscopic imaging might have confirmed a clinical diagnosis of GPA.

On the basis of the clinical picture and diagnostic tests, a diagnosis of a severe form of GPA was established and a decision to use cyclophosphamide was made.

From May 2011 to March 2012 the patient received eleven cyclophosphamide pulses (total dose over 12 g), combined with oral steroids. During the treatment several exacerbations were observed, with febrile states, worsening of cough and dyspnea, hemoptysis, and severe pain, requiring intravenous methylprednisolone pulses.

In addition, the patient required prolonged hospitalizations and intravenous antibiotics several times due to respiratory infections. A gradually increasing exertional dyspnea and fatiguing coughing were observed. The symptom most difficult to cope with was severe pain in the face and forehead, requiring the administration of opioid analgesics.

Radiological examinations revealed a gradual progression of lesions in the lungs, up to large nodular infiltrates widespread on both sides. In February 2012, the control c-ANCA titre was found to have remained high (148 RU/ml).

There was no evidence of renal lesions. Regarding the failure of the treatment and the clinical progression of the disease, the patient was consulted at the Department of Rheumatology, University of Medical Sciences in Poznan. The use of rituximab was then recommended.

In April and May 2012 the patient received rituximab at the regimen of 375 mg/m^2 iv weekly (4 doses), with good tolerance.

One month later, a high resolution chest CT found maintenance of diffuse infiltrates on both sides, as well as nodular lesions with a halo. Bronchofiberoscopy revealed numerous cicatricially narrowed bronchi, from which purulent contents were coming out. Pulmonary function tests showed combined respiratory disturbances with a dominant severe restriction and significant reduction in carbon monoxide diffusion capacity (DLCO).

Although in radiological imaging and endoscopy, advanced lesions were still present, the patient's clinical condition had improved significantly. As the pain visibly decreased, it became possible to reduce doses of analgesics to half of those previously used. Dyspnea and cough also decreased, so the patient no longer required bronchodilators and cough suppressants.

In the following assessments at 3, 6 and 8 months after the rituximab therapy, further clinical improvement was observed. The patient's exercise capacity improved significantly. Dyspnea declined, and cough occurred only sporadically and was not accompanied by expectoration of sputum, or haemoptysis. The pain in the head and face did not occur, allowing the discontinuation of narcotic analgesics. Clinical improvement was also reflected in radiological imaging (Figure 2A, 2B) and pulmonary function tests.

The lesions in the ears, nose and sinuses appeared less respondent to the treatment. In the meantime, heart MRI (performed because of an episode of pulmonary embolism) revealed granulomatous lesions in the patient's heart (Fig. 3).

In peripheral blood flow cytometry performed 3, 6 and 8 months after the rituximab therapy the percentage of CD20 + cell was 0%.

Moreover, c-ANCA titre was undetectable. Given a spectacular clinical effect and good tolerance of the treatment, rituximab maintenance therapy was considered.

Unfortunately, the patient developed a generalized infection preceded by the respiratory tract infection. He was admitted to the intensive care unit at municipal hospital, where, within 24 hours, he developed a multiorgan failure and died.

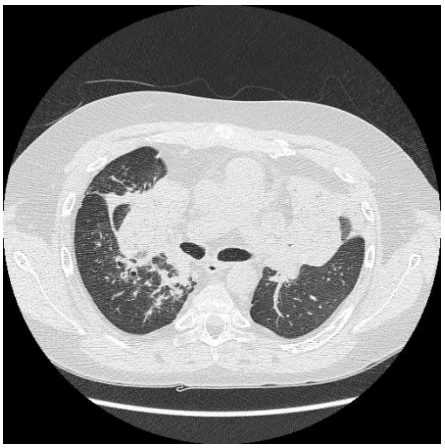

Fig. 2A. High resolution CT of the chest, before the treatment with rituximab. In both pulmonary fields visible widespread infiltrations forming perihilar masses (thick arrow) and numerous nodules disseminated in both lungs (thin arrows)

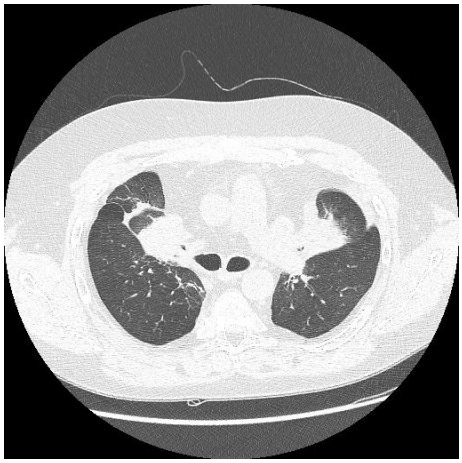

Fig. 2B. High resolution CT of the chest performed 6 months after the administration of rituximab. Remarkable reduction of the perihilar infiltrations (arrows) and the number of nodules

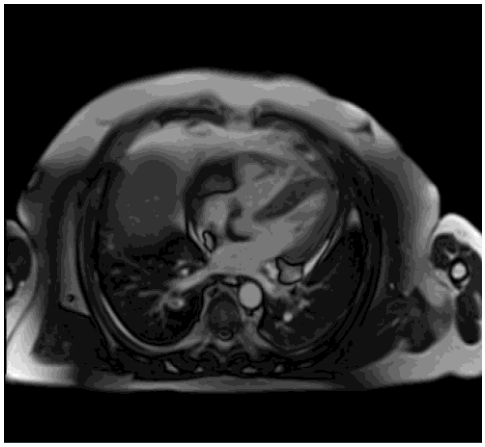

Fig. 3. Heart MRI shows the presence of several granulomas in the pericardium (arrows)

DISCUSSION

In the case presented, granulomatosis with polyangiitis (GPA) was characterized by an aggressive course with progressive, massive sinus and pulmonary involvement. The clinical course of GPA in children is slightly different from the described in adults. Nasal discharge, septal perforation, sinusitis are observed in about 83% of patients [5,6]. Pulmonary involvement is noted in 73% versus up to 90% of adult patients [7]. Symptoms more often observed in children than in adults are subglottic tracheal stenosis (18%) and saddle nose deformity (15%) [5,6].

The incidence of GPA in children is lower than in adults [3], although there are papers showing an increase in occurrence of the disease of children [4]. In the patient described the combination of affected organs at diagnosis seems typical for GPA, but the unusually early presentation of the rare disease made the diagnosis particularly difficult.

Standard treatment of generalized GPA includes cyclophosphamide and steroids. There is the eventuality of the use of a number of other drugs, including rituximab - a biological agent, which is a monoclonal chimeric human-murine antibody that reacts with the CD20 surface antigen of B and pre-B lymphocytes [8]. Rituximab is currently the best studied biological agent in the therapy of GPA. After administration of the drug rapid depletion of B cells can be observed, as well as decrease in ANCA titer [9]. In the patient we observed such changes in laboratory parameters at 3 months after administration. The percentage of CD20 + cells was 0%, and ANCA were undetectable. The laboratory improvement occurred simultaneously with the clinical recovery.

Currently, we have data from two randomized controlled trials comparing the efficacy and safety of rituximab and cyclophosphamide in the treatment of patients with generalized forms of GPA: RITUXVAS and RAVE [10,11].

Both studies have demonstrated the comparable efficacy of rituximab and cyclophosphamide in the induction of remission. Moreover, RAVE trial revealed its better efficacy in the group of patients who experienced relapses of the disease. Stone et al. reported 64% of remissions in the whole group of patients treated with rituximab (vs 53% in the group treated with cyclophosphamide) and 67% vs 42% in the patients with history of previous relapses [11].

In the studies rituximab was administered in a dosage regimen of 4 weekly doses of 375 mg/m2 iv, which was also used in the described patient. The percentage of adverse events was similar in patients treated with rituximab and cyclophosphamide. The most common adverse events, as in earlier studies [9] were infections (including severe) and leukopenia [10,11]. Secondary malignancies were

also observed. So, although serious complications of rituximab therapy are relatively rare, they should also be taken into account, and patients receiving this treatment ought to be carefully monitored.

Due to its high efficiency and satisfactory safety profile, rituximab is mentioned in the current recommendations of EULAR as a remission-inducing drug in generalized and severe forms of GPA, equivalent to cyclophosphamide, especially as an alternative option for relapsing or refractory disease [8]. Moreover, the results of a recently published study on the use of rituximab in the maintenance therapy of GPA are encouraging. Guillevin et al. [12] presented the efficacy of repeated doses of rituximab in the prevention of relapse and an acceptable safety profile. Maintenance treatment with rituximab seems an interesting option for patients with relapsing disease.

Holle et al. [13] reported better effects of treatment with rituximab in cases with lesions of vasculutis type, but less visible in relation to granulomas and lesions located in the orbit. This tendency was also reflected in the described patient's clinical course – despite a spectacular improvement in the pulmonary symptoms of the disease, features of upper airway and ear involvement persisted.

In conclusion, the case described illustrates difficulties in diagnosing GPA. Moreover, it shows how biological agents, including rituximab, are extending the therapeutic options for patients with GPA, and that they are a promising new tool in the treatment of severe forms of the disease.

However, many issues related to the biological treatment of GPA, including safety and the best schedule of monitoring, still remain open.

CONCLUSIONS

GPA is an interdisciplinary problem, often difficult in diagnosis and treatment. The introduction of biological agents, such as rituximab, has extended the therapeutic options for patients with severe forms of GPA. However, many issues related to the biological treatment, including safety and the best schedule of monitoring, still remain open.

Conflicts of interest

Nothing to declare

Financial Disclosure/Funding

Nothing to declare.

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