ranulomatosis with polyangiitis (GPA), previously known as Wegener’s granulomatosis (WG) is a necrotizing vasculitis involving small and medium sized vessels with the formation of non-caseified granulomas in involved organs. It represents a systemic disease that may affect many organ systems together with formation of granulomatous inflammation, although upper-lower respiratory tract and renal involvement are typical for this disorder. In this report, we describe a child with type 1 diabetes mellitus who was diagnosed with GPA based on respiratory signs and symptoms. The coexistence of these two conditions has never been reported in our country.
**CASE REPORT**

A 17-year old female patient previously diagnosed with type 1 diabetes mellitus and uveitis admitted to our Pediatric Pulmonology Outpatient Unit with complaints of hoarseness and shortness of breath. When she was 15 years old, she had undergone nasal endoscopy at the ear-nose-throat outpatient unit as well as paranasal computed tomography (CT) examination due to complaints of nasal pain and edema. Upon a diagnosis of maxillary and frontal sinusitis, she had been given treatment with oral antibiotics and nasal corticosteroid spray. In the following 2 month period, although symptoms improved, she developed a nasal deformity (Figure 1). Later, she developed redness in her eye and was found to have diffuse hyperemia, increased vascularity, tortuosity and dilatation in her sclera, suggesting a pre-diagnosis of scleritis. An orbital ultrasonography (US) was performed showing vitreal hemorrhage, slightly increased echogenicity and a scleral thickness of 1.9 mm leading to a diagnosis of scleritis. She was referred to the department of rheumatology after experiencing polyuria, polydipsia, weight loss of 7 kg within 6 month period, hair loss, pain in the shoulder and elbow joints and respiratory symptoms. At that time her laboratory results were as follows: WBC 15.470 /mm³; ANS: 12550/mm³; platelets 611.000/mm³; CRP 3.2 mg/dl; ESR 40 mm/hr; ANA dilution /screening and identification negative; anti-neutrophil cytoplasmic antibody (ANCA) negative; HLA B27 and B51 negative. Her urinalysis showed (++++) glucosuria and she had a fasting blood glucose of 204 mg/dl with subsequent referral to pediatric endocrinology unit. Control blood sugar was 319 mg/dl, HbA1c was 10%, Anti-GAD (glutamic acid decarboxylase) was 275 IU/ml (range; 0-30 IU/ml) positive and she was placed on insulin therapy with a diagnosis of type 1 diabetes mellitus (DM). She continued to have shortness of breath and she underwent a nasal endoscopy in an external health facility during which she developed respiratory arrest, intubated and admitted to the intensive care unit. After her discharge, she was diagnosed with asthma and treatment with inhaled steroids were started. She was referred to our unit due to the absence of response to therapy. Her past medical history was unremarkable while her family history revealed a 1st degree parental consanguinity. Physical examination showed the presence of saddle nose and basal rhonci on auscultation in the left lung. Respiratory function tests showed fixed obstruction. Nasopharyngoscopy examination revealed a mass lesion narrowing the submucosal passage was identified in the inferior part of the left arytenoid cartilage (Figure 2). Cervical CT showed defects and irregularity in the cricoid cartilages at level of larynx as well as fracture and irregular borders in the thyroid cartilage. High

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**FIGURE 1:** Saddle-nose deformity.

**FIGURE 2:** A mass lesion associated with the narrowing of the submucosal passage in the inferior part of the left arytenoid cartilage.
resolution computed tomography (HRCT) revealed focal narrowing and increased wall thickness in the proximal left main bronchus; and pulmonary nodules in the lateral superior lobe of the right lung (4.5 mm in diameter) and in the lateral left lower lobe (1.5 mm in diameter). Biopsy of the larynx mucosa revealed no pathology. A diagnosis of granulomatous polyangiitis was made based on the upper respiratory tract involvement (saddle nose defect, chronic sinusitis), laryngo-tracheobronchial involvement (subglottic and bronchial stenosis) and pulmonary involvement (pulmonary nodule). Initially, pulsed intravenous methylprednisolone (30 mg/kg/day, max 1 g) was given for 3 days, followed by azathioprine (2 mg/kg/day) and oral prednisolone (1 mg/kg/day). Currently she is through 11 months of follow-up with improvement of shortness breath and prednisolone is tapered to 5 mg/day.

**DISCUSSION**

GPA most frequently occurs in individuals between 45 and 60 year of age, while it is a rare condition in the pediatric age group (2.7-6.3 case/million years). In a study conducted by the Turkish Pediatric Vasculitis Working Group, only one pediatric case of GPA was detected over a 5-year period. Genetic predisposition, infections as well as environmental and pharmacological agents are implicated in the etiology of this condition through induction of the release of pro-inflammatory cytokines and inflammatory responses involving ANCA. ANCA positivity and responsiveness to immunosuppressive agents are supportive of an autoimmune process underlying this condition. Two subtypes of GPA have been defined: systemic and localized. The localized form is generally limited to upper respiratory tract involvement. In a study by Stone et al. patients with the localized disease were nearly a decade younger at disease onset compared with patients with systemic disease, suggesting that children with GPA are more likely to present with localized disease. Detection of ANCA positivity through immunofluorescence assay and enzyme immunoassorbent assay provides high sensitivity and specificity for the disease. However, ANCA can be negative in up to 40% of pediatric cases, particularly those with the localized form of the disease. Similarly, our patient had the localized form of the disease and had ANCA negativity.

Recently new criteria for childhood GPA/WG have been established and validated by the European League Against Rheumatism/Paediatric Rheumatology International Trials Organisation/ Paediatric Rheumatology European Society (EULAR/PRINTO/PRES) (Table 1). Subglottic, tracheal or endobronchial narrowing as well as the presence of c-ANCA or PR-3 ANCA were incorporated into diagnostic criteria. A diagnosis requires at least three of these six criteria. Accordingly our patient had three criteria including upper respiratory tract, laryngo-tracheobronchial and pulmonary involvement.

Until now, only two patients with coexistent type 1 DM and GPA have been reported. To the best of our knowledge, no such cases have been reported in our country previously. Of the two cases previously reported elsewhere, the first was a 14-year-old girl with newly diagnosed type 1 diabetes and GPA, presenting in a limited form with maxillary and sphenoidal sinuses and central nervous system granulomas. Sugimoto et al. suggested that their patient had GPA-triggered immunological abnormalities leading to insulitis, as evidenced by the presence of islet cell surface antibodies (ICSA), which ultimately led to the development of type 1 DM. The second case was a 14 year old boy, who was diagnosed with type 1 DM at 7 years of age. He had presented with pulmonary

<table>
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<th>TABLE 1: Classification criteria for Wegener’s granulomatosis.</th>
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<td>Granulomatous inflammation on biopsy</td>
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<tr>
<td>Abnormal urinalysis*</td>
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<td>Nasal sinus inflammation</td>
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<tr>
<td>Subglottic, tracheal or endobronchial stenosis</td>
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<td>Abnormal chest x ray or computed tomography</td>
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<td>PR3 ANCA or C-ANCA staining</td>
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<td>*Haematuria and/or significant proteinuria.</td>
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hemorrhage, deep anemia (Hb of 4.4 g/dl), and acute renal failure and experienced complete resolution of the signs and symptoms 3 weeks after admission with therapy including pulsed methylprednisolone, cyclophosphamide and RBC transfusion. In our case, the diagnostic interval between GPA and Type 1 DM was shorter and we believe that the pathogenesis could involve the mechanisms proposed by Sugimoto et al. for their patient.

Prior to the introduction of glucocorticoids and cyclophosphamide, GPA had a fatal outcome in most adult and pediatric patients, with a 1 year mortality of 80%, mostly due to renal or pulmonary failure or infection. Currently, due to the absence of clinical pediatric studies examining therapeutic options for pediatric GPA patients, adult treatment protocols are being utilized for children. Oral therapy with cyclophosphamide and glucocorticoids for more than 2 years is associated with remission rates around 90% in adult or pediatric patients. Depending on the severity of the disease, the treatment may be divided into two phases as remission induction and remission maintenance. Prednisone, cyclophosphamide, plasma exchange and methotrexate are used for induction, while maintenance may be achieved with prednisone, methotrexate, azathioprine and leflunomide. Since our patient had localized form of GPA, induction was carried out with IV pulse steroid followed by the use of azathioprine and oral steroid for remission.

In conclusion, GPA in pediatric patients may be associated with a diagnostic delay, since it is a rare condition that may mimic more frequent diseases of childhood such as otitis, sinusitis, upper respiratory tract infections, asthma and conjunctivitis in its initial phase. In patients who progress during therapy and who have concomitant lower and upper respiratory tract involvement, a diagnosis of GPA should also be considered in differential diagnosis. On the other hand, it should also be borne in mind that this clinical entity responds dramatically to treatment with systemic steroids and immunosuppressive agents, while it may be associated with significant morbidity and mortality when treatment is delayed.

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Conflict of Interest
No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

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