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Acute laryngeal dyspnea as first presentation of granulomatosis with polyangiitis

Ostra duszność krtaniowa jako pierwszy objaw ziarniniakowatości z zapaleniem naczyń

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Abstract

Granulomatosis with polyangiitis (GPA) is a multi-organ disease which mostly affects lungs, kidney, and head and neck region. We report a rare case of acute laryngeal dyspnea and rapidly progressive pulmonary changes as first manifestations of disease. A 53 year-old woman presented with symptoms of two-week dyspnea, which aggravated rapidly in the preceding hours. Laryngological examination revealed subglottic infiltrations and vocal fold oedema which required urgent tracheotomy. During few days she developed gingival ulcerations and pulmonary infiltration with negative serum c-ANCA titers. The histopathological examination of subglottic and gingival biopsies and the clinical picture established the diagnosis of GPA. She was treated with prednisone and cyclophosphamide with recovery; however, during over 3 years of follow-up, pulmonary symptoms relapsed and subglottic stenosis persisted. The difficulties in diagnosis and treatment in this unusual presentation of GPA are outlined with conclusion that in patients with subglottic infiltration, which develops rapidly, even when this is a sole presentation of the disease, and when c-ANCA are negative, GPA should always be considered.

Key words: granulomatosis with polyangiitis, subglottic stenosis, pulmonary symptoms

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Streszczenie

Ziarniniakowatość z zapaleniem naczyń (GPA) jest wielonarządową chorobą, która najczęściej dotyczy płuc, nerek oraz regionu głowy i szyi. Autorzy przedstawiają rzadki przypadek ostrej duszności krtaniowej jako pierwszego objawu choroby. Kobieta lat 53 zgłosiła się z powodu trwającej od 2 tygodni duszności, która nasiliła się znacznie na kilka godzin przed przyjęciem. W badaniu laryngologicznym stwierdzono naciek okolicy podgłośniowej i obrzęk fałdów głosowych, wymagające pilnej tracheotomii. W kolejnych dniach u chorej wystąpiły owrzodzenia dziąseł i nacieki w płucach, przy braku obecności przeciwciał c-ANCA. Na podstawie badania histopatologicznego wycinków z okolicy podgłośniowej i dziąseł oraz obrazu klinicznego ustalono rozpoznanie GPA. W leczeniu zastosowano prednison z cyklofosfamidem i uzyskano poprawę, w okresie ponad 3-letniej obserwacji wystąpił jednak nawrót objawów płucnych, utrzymywało się zwężenie podgłośniowe. W pracy zwrócono uwagę na trudności w postępowaniu diagnostyczno-terapeutycznym podkreślając rolę podgłośniowego obrzęku krtani jako jedynej początkowo manifestacji GPA, nawet przy braku obecności przeciwciał c-ANCA.

Słowa kluczowe: ziarniniakowatość z zapaleniem naczyń, zwężenie podgłośniowe, objawy płucne

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Introduction

Granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis), an autoimmune disorder characterized by necrotizing granulomatous inflammation of small-to-medium vessels, is a part of ANCA (antineutrophil cytoplasmic antibodies)-associated vasculities (AAV), which includes also eosinophilic granulomatosis with polyangiitis (eGPA, formerly Churg-Strauss syndrome) and microscopic polyangitis (MPA).

GPA is a multi-organ disease which mostly affects lungs, kidneys, and head and neck region. The nose and paranasal sinuses are the commonest sites of head and neck involvement at the initial presentation of GPA (in the form of nasal septal perforation, chronic rhinosinusitis, epistaxis, saddle nose deformity). The other locations like ear, eye and larynx are far less common [1]. We report a rare case of acute laryngeal dyspnea and rapidly progressive pulmonary changes as first manifestations of disease. The institutional review board of the Medical University of Lodz has approved the publication of this case report.

Case report

Female 53 year-old smoker (20 pack-years) was admitted to the Otolaryngology Department due to two-week dyspnea, which aggravated rapidly in the preceding hours. Laryngological examination revealed subglottic infiltration and vocal fold oedema (Fig. 1). Initial laboratory tests showed high white blood cells (WBC) (25.0 G/L, 74.5% of neutrophils) and C-reactive protein (74.9 mg/l) levels. Urgent tracheotomy and laryngoscopy with biopsy of subglottic lesions were performed. On the fifth day of the postoperative period, patient's body temperature rose, and after next 2 days she developed erosive and haemorrhagic lesions on gingiva, from which biopsy was taken. First chest X-ray was normal, but the second one, 5 days later, demonstrated upper right lobe cavitating infiltration (12 × 32 mm). Both sugblottic and gingival biopsy revealed high intensity chronic inflammation and mild epithelial dysplasia with ulceration and granulation, highly suggestive of GPA. Serum c-ANCA was negative. Patient was transferred to Department of Pneumonology and Allergy, where chest computed tomography (CT) revealed thick-walled cavities of different size in the lungs, with few subpleural nodules and slightly enlarged subcarinal lymph nodes (13.5 mm in diameter) (Fig. 2). Laboratory results showed persistent increase

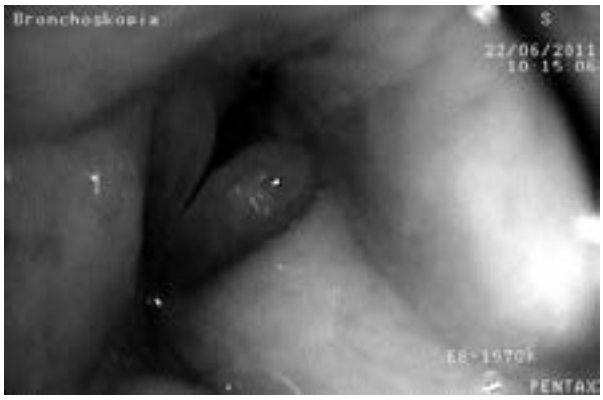

Figure 1. Bronchoscopic image 5 days after patient's admission indicating vocal fold oedema and subglottic infiltration

Rycina 1. Obraz bronchoskopowy w 5-tym dniu po przyjęciu chorej do szpitala — obrzęk fałdów głosowych i naciek okolicy podgłośniowej krtani

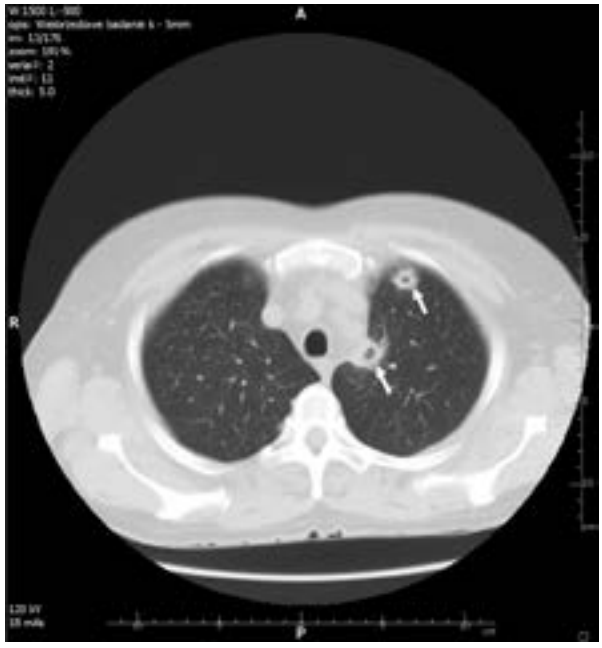

Figure 2. Chest computed tomography — two infiltrations with cavitations in the upper left lobe (indicated by arrows)

Rycina 2. Badanie tomografii komputerowej klatki piersiowej — dwa nacieki z rozpadem w górnym płacie lewego płuca (strzałki)

of inflammatory markers: C-reactive protein (30 mg/l) and WBC (19.0 G/L). At the beginning antibiotics were introduced, but after biopsy results had become available, prednisone (1 mg/kg) and cyclophosphamide (CYC, 2 mg/kg) were started. The patient slowly recovered, but one year later, when prednisone was tempered to 10 mg per day and CYC was replaced with azathioprine (AZA), symptoms relapsed. She presented progressive dyspnea with new infiltrations on

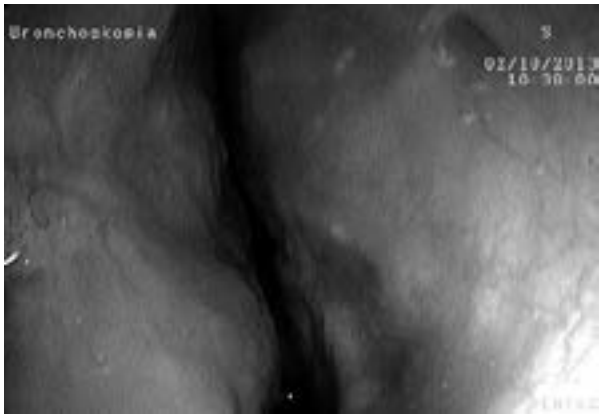

Figure 3. Bronchoscopic image showing protracted subglottic stenosis

Rycina 3. Obraz bronchoskopowy — przetrwałe zwężenie podgłośniowe

chest X-ray. The level of c-ANCA at that time was slightly increased (titer 1:32). Treatment with AZA and prednisone was intensified and resulted in good clinical response. At present she is continuing treatment (AZA 150 mg/day + prednisone 10 mg/day). During over 3 years of follow-up she had several bronchofiberoscopic examinations, which have shown the gradual regression of subglottic infiltration, with residual stenosis allowing only the passage of the bronchoscope to trachea (Fig. 3). Patient did not consent to any dilatation procedures; however, she has removed tracheostomy tube few months ago and breathes without it.

Discussion

Upper respiratory tract involvement has been reported in 75–93%, and pulmonary involvement in 60–85% of patients with GPA [2]. The main finding on chest CT are bilateral nodules and cavitating infiltrations. Vasculitis-related severe diffuse alveolar haemorrhage may also occur. Subglottic stenosis may develop in 7–23% of cases, and is very rare as a presenting feature, found only in 1–6% [3–5]. Such presentation with life-threatening subglottic stenosis is more common in younger patients than in patients with multiorgan GPA [6]. In the reported case, fulminant clinical course requiring tracheotomy was followed by the rapid development of lung changes.

Although the exact etiology of GPA still remains unclear, ANCA, especially c-ANCA (cytoplasmic immunofluorescence pattern) are highly specific and sensitive to this disease, thus suggesting their pathogenic role in the development of the disorder. Proteinase 3-ANCA (PR 3-ANCA,c-ANCA) and myeloperoxidase-ANCA (MPO-ANCA, p-ANCA) can activate neutrophils, enhance their adhesion to endothelial cells, resulting in release of reactive oxygen species and lytic enzymes which damage vessel walls. Recently, it was found that the number and function of T regulatory lymphocytes CD4+CD25+FoxP3+Treg were decreased in patients with GPA as compared to healthy controls. Moreover, increased proportion of Treg lymphocytes was associated with more rapid remission [7]. The role of B-lymphocytes as anti PR 3-ANCA producing IgG is more clear. These cells were found in close proximity to PR-3 positive cells in the sites of granulomatous inflammation. As a trigger for GPA, environmental factors as well as infections and/or nasal carriage of *Staphylococcus aureus* should be considered [8]. It is well documented that about 25–40% of patients, mainly those with limited GPA, have undetectable ANCA [4, 9] and this was at the beginning in our case.

In presented case, after introducing CYC and corticosteroids, regression of the pulmonary changes was observed. Conventional immunosuppressive therapy is powerful enough to produce a remission in 90% of patients, but relapses of the disease are common [6]. There are some data suggesting that trimethoprim-sulfamethoxazole may be beneficial in reducing trigger factors contributing to exacerbation of GPA, mainly in patients with localized disease [10]. Recently, in severe refractory GPA, rituximab — monoclonal antibody against CD20 (B lymphocytes) has become the first-line agent for remission induction and to prevent relapses in chronically relapsing patients [11].

An important observation from the presented case is, that subglottic stenosis persists or even progresses, despite otherwise effective immunosuppressive treatment. It has been reported that only about 20–26% of patients improve after systemic treatment, while the remaining patients may require local surgical interventions [5]. The therapeutic options for subglottic stenosis consist of endoscopic dilatation, endoscopic laser excision or surgical resection of involved segment followed by reconstruction [5, 12]. Using endoscopic technique to remove a stenotic part with subsequent soaking of these areas with mitomycin-C (due to its antifibroblastic activity), Arebro et al. [13] reported an overall success rate of 85%. Langford et al. [3] proposed new technique based on intralesional long-acting corticosteroid injection which seems more effective local therapy in subglottic stenosis [4, 14, 15].

In conclusion, in patients with subglottic stenosis, which develops slowly or rapidly, even when this is a sole presentation of the disease, and when c-ANCA are negative, GPA should always be considered.

Conflict of interest

The authors declare no conflict of interest.

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