



Connecting the dots – rapid diagnostic process for eosinophilic granulomatosis with polyangiitis in a patient with hemoptysis

Adam Krusiński^{1,A-B,E-F}, Katarzyna Redestowicz^{1,B-D,F}, Dorota Daniluk^{2,B-D}, Julia Gontarz^{2,B-D}, Pola Bakalczuk^{2,B-D}, Justyna Emeryk-Maksymiuk^{3,D-F}, Anna Grzywa-Celińska^{1,D-F}

¹ Chair and Department of Pneumology, Oncology and Allergology, Medical University, Lublin, Poland

² Student Research Association of Pulmonology, Chair and Department of Pneumology, Oncology and Allergology, Medical University, Lublin, Poland

³ Chair of Internal Medicine and Department of Internal Medicine in Nursing, Medical University, Lublin, Poland

A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

Krusiński A, Redestowicz K, Daniluk D, Bakalczuk P, Emeryk-Maksymiuk J, Grzywa-Celińska A. Connecting the dots – rapid diagnostic process for eosinophilic granulomatosis with polyangiitis in a patient with hemoptysis. J Pre-Clin Clin Res. doi: 10.26444/jpccr/149952

Abstract

Introduction. Eosinophilic granulomatosis with polyangiitis (eGPA) is a rare type of vasculitis. We described the case of the patient who was admitted to our Department due to haemoptysis, in whom the model-based clinical reasoning and quick diagnostic process led to the diagnosis and referral of the patient to specialists dealing with the treatment of this disease. We wanted to emphasize the fact that the patient developed symptoms of the disease many years before diagnosis. However, these clinical problems were treated individually. A broader reflection of the patient's symptoms may have led to earlier diagnosis and implementation of adequate treatment.

Objective. The aim of the study is to underline the importance of clinical reasoning on the example of eGPA model diagnostics. The combination of several clinical findings led to the correct diagnosis, which enabled the patient to obtain treatment and improved further prognosis.

Key words

diagnostics, eosinophilic granulomatosis with polyangiitis, haemoptysis, anti-neutrophil cytoplasm antibody-associated vasculitis

INTRODUCTION

Eosinophilic granulomatosis with polyangiitis (eGPA), formerly known as Churg-Strauss syndrome, is one of the systemic vasculitis characterized by peripheral eosinophilia, asthma, and allergic inflammation of the upper respiratory tract.

The study presents the diagnostic process of eGPA of a patient who presented to our Department due to haemoptysis.

EGPA is classified as a systemic necrotizing small-to-medium calibre vasculitis [1] and is most often characterized by involvement of the organs, i.e. lungs, kidneys, peripheral nerves, blood and gastrointestinal tract. The eosinophilic infiltration in the vessel walls leads to loss of their integrity, thus possible bleeding, resulting in ischemia and necrotic changes in organs. The etiology of the disease is still unknown. The most common manifestations of the disease are severe late onset asthma, nasal polyps and allergic rhinitis, which may precede for many years before proper diagnosis.

OBJECTIVE

The aim of the study is to present the diagnostic process in a patient with haemoptysis, leading to the diagnosis of a very rare condition – eosinophilic granulomatosis with polyangiitis.

MATERIALS AND METHOD

The material for this case study was collected from real-life clinical process and medical records of the Chair and Department of Pneumology, Oncology and Allergology, at the Medical University in Lublin, Poland. The patient's personal data were anonymized. Such case reporting, according to local law, does not require the consent of the Bioethics Committee.

CASE STUDY

A 60-year-old patient was admitted to the Department of Pneumology, Oncology and Allergology due to haemoptysis lasting for two days. He reported three weeks of joint pain (knee, elbow, ankle, wrist), low-grade fever, and had been diagnosed with pneumonia ten days earlier, which required antibiotic treatment (amoxicillin). Ten years before he had been diagnosed with asthma, which was well controlled with inhaled drugs. In addition, it was particularly noted that he had repeatedly undergoing surgical procedures

Address for correspondence: Anna Grzywa-Celińska, Chair and Department of Pneumology, Oncology and Allergology, Medical University, ul. Jaczewskiego 8, 20-954 Lublin, Poland
E-mail: annagrzywacelinska@umlub.pl

Received: 03.04.2022; accepted: 10.05.2022. first published: 23.05.2022

to remove nasal polyps (eight, five and two years before current hospitalization).

Laboratory tests showed mild peripheral blood eosinophilia, increased levels of D-dimers and inflammatory markers, mild normocytic anaemia and haematuria (Tab. 1). No obvious signs of pulmonary embolism were found in angio-CT of the lungs, but changes suggesting vasculitis with possible alveolar haemorrhage were described (Fig. 1). Taking into account the features of vasculitis, peripheral blood eosinophilia, as well as the history of asthma and nasal polyps, eosinophilic granulomatosis with polyangiitis was suspected.

In the Department of Pulmonology, anti-haemorrhagic

Table 1. ?

Parameter	Result	Reference value
Leukocytes (x10 ⁹ /L)		4.0–10.0
(day 0)	15.8	
(day 1)	15.34	
(day 8)	12.58	
Haemoglobin (g/dl)		14.0–18.0
(day 0)	9.6	
(day 1)	9.5	
(day 8)	9.3	
Eosinophil count (x10 ⁹ /L)		0.05–0.5
(day 0)	3.37	
(day 1)	2.78	
(day 8)	0.49	
cANCA (PR-3)	0.7	negative<20 weak positive 21–30 positive>30
pANCA (MPO)	134.6	negative<20 weak positive 21–30 positive>30
Urine erythrocyte count	15–20	1–2 in the field of vision
Total IgE (IU/ml)	180.6	158.0
Creatinine (mg/dl)	1.0	0.7–1.3
Creatinine clearance (eGFR)	80.4	> 60 ml/min/1,73m ²
CRP (mg/dl)		0–5.00
(day 0)	75.22	
(day 1)	80.12	
(day 8)	14.49	

treatment (tranexamic acid, etamsylate, cold compresses on the chest, recommendations for bed regimen and avoidance of hot food and drinks), empirical antibiotic therapy (levofloxacin, piperacillin + tazobactam), hepatoprotective treatment was started. Extensive diagnostics focused on systemic vasculitis and alveolar bleeding were implemented. Increasing eosinophilia and high levels of perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) were stated.

Although the patient showed no symptoms of the cardiovascular system, he was consulted by a cardiologist, electrocardiographic examination (normal) and echocardiography were performed, which, apart from slight mitral regurgitation, did not reveal any significant abnormalities.

During hospitalization, an additional CT of the sinuses was performed, but there was no bleeding in the upper respiratory tract; however, no typical features of systemic vasculitis were found.

A very thorough history was collected of possible impairment of the functions of different organs and systems, but the patient did not report any other ailments.

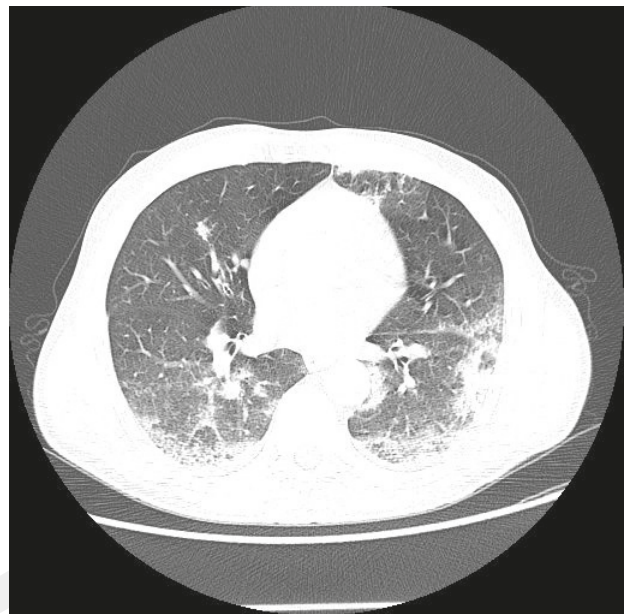


Figure 1.

Due to the unequivocal clinical picture, a routinely performed bronchofiberscopy in patients with haemoptysis was abandoned.

The patient was consulted by the rheumatologist, confirming the initial diagnosis of eGPA, three-day steroid pulses (methylprednisolone 1000 mg/day intravenously) were initiated, followed by treatment with oral prednisone at a dose of 20 mg/twice a day. The applied treatment resulted in the resolution of haemoptysis and haematuria, a satisfactory decrease in inflammatory parameters.

The patient was referred for further treatment at the Rheumatology Clinic, where, due to a temporary deterioration in kidney function, he was again given steroid pulses. The patient is currently treated with prednisone maintenance dose 1x10 mg, with no evidence of active disease.

DISCUSSION

Eosinophilic granulomatosis with polyangiitis, also known as Churg-Straus syndrome, is a rare, small to medium necrotizing vasculitis with eosinophilia and most often – asthma. The incidence of this disease worldwide ranges from 10.7–14/ million adults, the median age of onset 38–54 years [2].

Based on the presence or absence of ANCA antibodies, two types of this disease are distinguished – ANCA-positive and ANCA-negative [3]. ANCA-positive patients (37–47% of all cases) [3–9] are of more ‘vasculitic type’ – presenting weight loss, myalgia, migrating polyarthralgia, mononeuritis complex, glomerulonephritis, alveolar bleeding, and laryngological symptoms, but less frequently heart diseases [3]. The presence of antibodies is also associated with significantly more frequent relapses [3, 10]. ANCA-negative patients present eosinophilic phenotype more often and are prone to develop cardiac manifestations of the disease [2].

Among other ANCA-dependent systemic vasculitis (granulomatosis with polyangiitis GPA, microscopic polyangiitis – MPA), antibodies are the least common in eGPA [2].

Clinically, three stages of the disease can be observed. The prodromal phase, characterized by the onset of asthma, allergic rhinitis and nasal polyps, is the first to occur. Patients are often treated according to current asthma treatment guidelines, but may not achieve complete asthma control despite optimal treatment. Rhinosinusitis and nasal polyps are often present. It is quite characteristic that patients with EGPA are operated on repeatedly for nasal polyps. However polyps of the upper airways may occur in many other diseases, mostly in chronic rhinosinusitis, allergic fungal rhinosinusitis, and aspirin-exacerbated respiratory disease [11].

The second phase involves peripheral eosinophilia, which often goes unnoticed for months or even years, as happened in the current case study. The symptoms of systemic were conducted in the presented patient.

There are objective tools to assess disease activity in individual patients. One of the first tools allowing evaluation of the activity of the eGPA (but also nodal polyarteritis, microscopic polyangiitis) was the Five Factor Score (FFS), which takes into account five variables: renal dysfunction, proteinuria, involvement of the heart, gastrointestinal tract and central nervous system. The advantage of this scale is its simplicity, but it does not allow for prognosis of the course of the disease [12].

Another, most commonly used scale for assessing the activity of all types of vasculitis is the Birmingham Vasculitis Activity Score (BVAS). This scale consists of 66 variables (symptoms) ordered in nine modules for different organs. Each symptom has its own score depending on its clinical significance [12]. The BVAS is available now on the internet as a simple calculator.

As mentioned above, eGPA can involve many organs and systems. Cardiovascular symptoms are mostly associated with higher risk of death. According to Futura et al. [5], cardiovascular symptoms occur in 16–60% of patients. In the group of eGPA patients examined by Chen [13], cardiovascular symptoms occurred in 27.7% of cases. Cardiovascular symptoms of eGPA include acute pericarditis, constrictive pericarditis, heart failure, myocardial infarction, cardiomyopathy [10]. Patients with the cardiovascular system involvement in the course of eGPA tend to be younger at onset of the disease compared to those without cardiac problems, they have higher eosinophil count, higher disease activity in BVAS and poorer prognosis. In the cardiac involvement group, 43.5% of patients were asymptomatic, but cardiac abnormalities could be detected by examinations of the cardiovascular system [13]. In the current case, the patient did not present any symptoms or abnormalities in the cardiovascular system examinations. However, due to cardiovascular symptoms, patients with eGPA may be referred for cardiac diagnosis, which may delay diagnosis and appropriate treatment.

As complications from the nervous system can often have serious consequences for health and life, it was fortuitous that the patient in the presented case study did not have any symptoms indicating involvement of the nervous system. Central nervous system damage is the most common cause of death of patients with eGPA (intracerebral haemorrhages or cerebral vessels embolism) [14]. Injury to the central nervous system can also manifest as seizures, coma, orientation disorders [10], as well as characteristic mono-nerve complex inflammation (mononeuritis multiplex). Involvement of

cranial nerves: II, III, VII, VIII and the optic nerve is most often observed [10].

Kidney injury is quite common in ANCA-mediated inflammation which can lead to severe complications and even the need for renal replacement therapy. Necrotizing eosinophilic disease is the cause of feature segmental glomerulonephritis necrosis, in some cases with the formation of crescents [10]. In the current study, only transient non-significant haematuria observed. There was no evidence of kidney damage.

Skin symptoms that may appear in the course of EGPA, painful subcutaneous nodules on the scalp and symmetrically on the limbs, as well as: purpura, urticaria, macular or papular rash and, less often – purpura reticularis (livedo reticularis), tumour ulcers or blockages in the cutaneous vessels [10]. There were no skin symptoms in the presented patient.

Treatment of eGPA consists of pulses of cyclophosphamide or short-term steroid therapy, after which maintenance treatment is adjusted according to the tendency to relapse. There are also studies on the effectiveness of using mepolizumab in monthly cycles in steroid-dependent or relapsing disease. Mepolizumab is a humanized monoclonal antibody against interleukin-5, the main cytokine responsible for the development and viability of eosinophils, thus its administration significantly reduces the level of circulating eosinophils in the blood, thereby damaging the vascular walls. Until recently, mepolizumab has been used to treat severe eosinophilic asthma. Currently, mepolizumab has been approved for eGPA treatment. At both doses of 100 mg every four weeks and 300 mg every four weeks it was effective in control of respiratory EGPA manifestations, improvement in systemic disease activity and allowed reduction in the dose of glucocorticosteroids [15]. The recommended dose of mepolizumab is higher comparing to the dose used in treatment of asthma, and accounts for 300 mg administered subcutaneously once every four weeks.

The differential diagnosis of eGPA should include granulomatosis with polyangiitis (formerly Wegener's disease) and microscopic polyangiitis, which are also characterized by the presence of ANCA, but peripheral eosinophilia, rhinosinusitis and asthma are not typical for these diseases [2]. Moreover, in patients with high peripheral blood eosinophilia, the diagnosis of hypereosinophilic syndrome should be taken into account [1].

Moreover, haemoptysis reported by a patient may be of a variety of etiologies. It is necessary to exclude neoplastic infiltrates in the respiratory tract, tuberculosis, pulmonary embolism, haemorrhagic diathesis or foreign body aspiration.

CONCLUSION

In conclusion, it should be stated that the presented case study confirms the assumption that many patients with eGPA remain without a final diagnosis. It is probable that many of them circulate among various specialists, obtaining immediate reduction of symptoms as a result of the use of various types of therapy. However, only the proper diagnosis of the disease allows for optimal therapy. The symptoms of eGPA are non-specific which usually makes the diagnosis difficult and late.

It is worth paying attention to patients with asthma in whom it is difficult to reach disease control and who tend to

develop nasal polyps. Such a simple and cheap examination as total blood count may allow the identification of patients with suspicion of eGPA.

REFERENCES

1. Groh M, Pagnoux C, Baldini C, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management. *Eur J Intern Med.* 2015; 26(7): 545–53. <https://doi.org/10.1016/j.ejim.2015.04.022>
2. Chakraborty RK, Aeddula NR. Churg Strauss Syndrome. <https://www.ncbi.nlm.nih.gov/books/NBK537099/> (access: 2022.01.04).
3. Comarmond C, Pagnoux C, Khellaf M, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): clinical characteristics and long-term follow up of the 383 patients enrolled in the French Vasculitis Study Group cohort. *Arthritis Rheum.* 2013; 65(1): 270–81. <https://doi.org/10.1002/art.37721>.
4. Almaani S, Fussner LA, Brodsky S, et al. ANCA-Associated Vasculitis: An Update. *J Clin Med.* 2021; 10(7): 1446. <https://doi.org/10.3390/jcm10071446>.
5. Furuta S, Iwamoto T, Nakajima H. Update on eosinophilic granulomatosis with polyangiitis. *Allergol Int.* 2019; 68(4): 430–436. <https://doi.org/10.1016/j.alit.2019.06.004>.
6. Saku A, Furuta S, Hiraguri M, et al. Longterm Outcomes of 188 Japanese Patients with Eosinophilic Granulomatosis with Polyangiitis. *J Rheumatol.* 2018; 45(8): 1159–1166. <https://doi.org/10.3899/jrheum.171352>
7. Durel CA, Berthiller J, Caboni S, et al. Long-Term Followup of a Multicenter Cohort of 101 Patients With Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss). *Arthritis Care Res (Hoboken).* 2016; 68(3): 374–87. <https://doi.org/10.1002/acr.22686>
8. Moosig F, Bremer JP, Hellmich B, et al. A vasculitis centre based management strategy leads to improved outcome in eosinophilic granulomatosis and polyangiitis (Churg-Strauss, EGPA): monocentric experiences in 150 patients. *Ann Rheum Dis.* 2013; 72(6): 1011–1017. <https://doi.org/10.1136/annrheumdis-2012-201531>
9. Tsurikisawa N, Oshikata C, Kinoshita A, et al. Longterm Prognosis of 121 Patients with Eosinophilic Granulomatosis with Polyangiitis in Japan. *J Rheumatol.* 2017; 44(8): 1206–1215. <https://doi.org/10.3899/jrheum.161436>
10. Wiatr E, Gawryluk D. Primary systemic ANCA-associated vasculitis — recommendations concerning diagnosis and treatment. *Pneumonol. Alergol. Pol.* 2013; 81: 479–491.
11. Settiple RA, Peters AT, Chiu AG. Chapter 6: Nasal polyps. *Am J Rhinol Allergy.* 2013; 27: S20–5. <https://doi.org/10.2500/ajra.2013.27.3926>
12. Madej M. Ocena aktywności zapalenia naczyń. *Przegl Reumat.* 2008; 3–4: 9.
13. Chen Y, Guo X, Zhou J, et al. Cardiac Involvement in Eosinophilic Granulomatosis With Polyangiitis: A Retrospective Study in the Chinese Population. *Front Med (Lausanne).* 2020; 7: 583944. <https://doi.org/10.3389/fmed.2020.583944>
14. André R, Cottin V, Saraux JL, et al. Central nervous system involvement in eosinophilic granulomatosis with polyangiitis (Churg-Strauss): Report of 26 patients and review of the literature. *Autoimmun Rev.* 2017; 16(9): 963–969. <https://doi.org/10.1016/j.autrev.2017.07.007>.
15. Bettiol A, Urban ML, Dagna L, et al. European EGPA Study Group. Mepolizumab for Eosinophilic Granulomatosis With Polyangiitis: A European Multicenter Observational Study. *Arthritis Rheumatol.* 2022; 74(2): 295–306. <https://doi.org/10.1002/art.41943>