

EGPA: early diagnosis is better

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As compared with initial descriptions of eosinophilic granulomatosis and polyangiitis (EGPA) showing poor survival, patient outcomes have dramatically improved over the past 2 decades. At 1 and 5 years post-diagnosis, survival rates now exceed 90% and 85%, respectively [1-3]. Besides advances in the therapeutic management of EGPA, better awareness and recognition of this rare condition have clearly contributed to improved survival. Delayed diagnosis and initiation of appropriate treatments can indeed negatively affect overall prognosis and outcomes.

However, it should be acknowledged that the diagnosis of EGPA often remains challenging and in some cases can be confirmed only during the course of the disease. EGPA is a rare disease with an incidence of about 1 to 2 per million people and a prevalence of about 10 to 15 per million [4-6]. Hence, most physicians will not likely see more than a couple of EGPA cases during their career. Diagnostic criteria to help with early diagnosis are lacking. The 1990 American College of Rheumatology criteria included the most typical “full-blown” disease characteristics and aimed at classifying patients with already diagnosed and proven vasculitis into a disease category. The Chapel Hill nomenclature are useful to define EGPA among the medical community but cannot be used for diagnosis. More importantly, we lack a good biologic or radiologic test to detect early EGPA or confirm the diagnosis. Anti-neutrophil cytoplasm antibodies (ANCA) are present in only 30% to 40% of EGPA patients at diagnosis and/or during disease flare (mainly anti-myeloperoxidase perinuclear ANCA) [1, 7-9]. Increased blood eosinophil count can suggest disease but is lacking in specificity in that it can be observed in other conditions as well, including simple allergy. Serum level of immunoglobulin E (IgE) is also usually elevated, but this sign lacks specificity even more so than blood eosinophilia. Biopsy of an affected tissue thus remains the gold standard to support the diagnosis; it may show vasculitis, i.e.

inflammation of the blood vessel wall, mainly with eosinophils, with other more subtle but inconstant features such as fibrinoid necrosis or granulomas. However, biopsies can be invasive and, depending on the organ, can cause moderate but irreversible damage such as persistent localized numbness after a peripheral nerve biopsy. In addition, biopsies do not always show typical histologic features, depending on the organ and because vasculitis lesions are segmental (i.e., have a patchy distribution along blood vessels).

Hence, physicians should think earlier than later of the possibility of EGPA in several clinical settings described below and must not hesitate to refer patients to a vasculitis center for evaluation and further investigation if needed. As described by Lanham et al., in the early 1980s, EGPA may be divided into and progress in 3 stages [10]: asthma and/or recurrent nasal polyposis (stage 1), which indeed corresponds more to a background condition than EGPA if not a prerequisite to development of blood and tissue eosinophilia (stage 2), then EGPA with its vasculitis manifestations (stage 3). Early identification of these pre-EGPA stages may help prevent severe complications of EGPA and promote faster remission. However, not all patients will show progression through these 3 stages, and one should not over- or prematurely diagnose EGPA. Eosinophilic allergic asthma with nasal polyposis is indeed more frequent than EGPA, and EGPA will not develop in most patients with allergic asthma [11].

The most frequent clinical settings that should alert physicians (and patients) to the possibility of EGPA are relatively easy to identify and remember.

- Asthma, especially late-onset asthma (i.e., starting in adulthood), that gradually worsens and becomes refractory to usual antiasthma drugs, with increased eosinophilia on white blood cell count. In most of these cases, allergic asthma or allergic bronchopulmonary aspergillosis is diagnosed, but early stages of EGPA can present in this way.
- Recurrent bronchitides and/or “pneumonias” in a patient with background asthma, especially late-onset asthma, with increased eosinophilia on white blood cell count. In most of these cases, “simple” infection, allergic bronchopulmonary aspergillosis or eosinophilic pneumonia is diagnosed, but early stages of EGPA can present in this way.

- Worsening, lingering and/or recurrent sino-nasal polyposis and/or sinusitis, especially if associated with (late-onset) asthma, with increased eosinophilia on white blood cell count. These manifestations are not sufficient for a diagnosis of EGPA because of no vasculitis, but early stages of EGPA can present in this way.
- Recurrent skin rash (any type) or hives with increased eosinophilia on white blood cell count. In most of these cases, simple allergy or chronic urticaria is diagnosed, but early stages of EGPA can present in this way and many different types of skin lesions can occur in EGPA (Figures 1 to 4).
- In a patient with asthma and/or sino-nasal polyposis, any symptoms of systemic vasculitis, including skin purpuric rash, numbness, tingling or weakness in hands or feet (mononeuritis multiplex), scleritis (or episcleritis), or renal disease (microscopic hematuria being the first manifestation of glomerulonephritis). Other possible and/or more severe manifestations, such as coronary arteritis or gut perforations due to inflammation and occlusion of the small vessels of the bowels, are rare features of EGPA that are more easily considered related to vasculitis (EGPA or another type of vasculitis).
- In a patient with asthma and/or sino-nasal polyposis, any new or worsening general or constitutional symptoms, including fever, joint pain, diffuse muscle pain, major involuntary weight loss, chest pain, palpitations or abdominal pain. These symptoms are not specific but may be the first signs of a vasculitis, including EGPA.

In such cases, it is wise to control blood cell count, including eosinophil count; check some inflammatory signs such as level of C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR); and perhaps order an ANCA screening test as well as other investigations according to the clinical presentation (e.g., chest X-ray or CT with respiratory symptoms; CT scan of sinuses with ear nose, and throat manifestations [Figure 5]; electromyography of peripheral nerve conduction with numbness; electrocardiography and cardiac imaging). Biopsies of skin lesions are easy to perform but may show non-specific leucocytoclastic vasculitis. The sensitivity of sinus biopsy is low (<50%).

Other biopsies, such as of a peripheral nerve or lung lesion, may be considered depending on the clinical presentation and after review of all obtained results, which may be sufficient to consider the diagnosis of EGPA highly probable for starting the appropriate treatment.

As with other vasculitides, such as giant cell arteritis, starting systemic corticosteroid treatment early, which remains the cornerstone of EGPA treatment, should not be considered a mistake, at least after all the appropriate diagnostic investigations have been realized (especially to rule out parasitic infections that can cause blood eosinophilia). Corticosteroids alone may still be insufficient to prevent more severe vasculitis complications, such as those listed in the original 1996 five factor score (i.e., cardiomyopathy or central nervous system, severe gastrointestinal or renal involvement [creatinine level > 140 $\mu\text{mol/l}$ or proteinuria > 1 g/24 hr] [12]. Physicians should remain alert to such severe complications and follow patients closely for early detection. Conversely, corticosteroid treatment should not be prolonged in the absence of a clear diagnosis. The diagnosis of EGPA should not be made too easily (and erroneously) for the (rare) patients with allergic asthma who depend on systemic corticosteroids for asthma control but who never had any other (vasculitis) manifestations, simply because they are corticosteroid-dependent. A corticosteroid-sparing agent can still be considered for such patients with intractable asthma. Of note, the discontinuation of corticosteroids in these patients with intractable asthma, sometimes after a successful trial with other anti-asthma drugs such as a leukotriene receptor antagonist, may unmask vasculitis manifestations (i.e., a “forme fruste” of EGPA) [13-15].

Studies may eventually identify more specific and sensitive biologic markers that will help in the early diagnosis of EGPA and in differentiating EGPA from mimicking diseases such as common allergic asthma, allergic bronchopulmonary aspergillosis, eosinophilic pneumonia or primary hypereosinophilic syndrome. Several potential biologic candidates have been investigated and include eotaxin-3 (CCL26), interleukin 5 (IL-5), IL-25, eosinophil cationic protein, and thymus and activation-regulated chemokine (TARC or CCL17) but with relatively disappointing results or that need to be validated in a larger number of patients with EGPA or mimicking conditions [16-19]. Because EGPA is a rare disease, achieving reliable and

reproducible results will take some time. Until then, effort must continue to improve awareness of this condition, systematize the diagnostic approach and investigations, optimize treatments for severe manifestations, reduce cumulative corticosteroid exposure and limit treatment-related side effects.

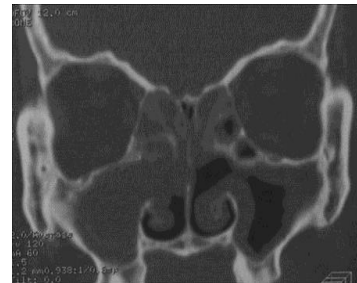
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Figures 1 to 4: Possible lesion types in EGPA: purpuric and ulceronecrotic lesions on both legs (1, top left), diffuse erysipelas-like rash with subcutaneous nodules (circle) on one leg (2, top right), pseudo-urticarial hive-like (itchy) lesions on one arm (3, bottom left), and macular erythematous and purpuric rash on one leg (4, bottom right) from 4 different patients.



Figure 5: CT scan of sinuses showing bilateral maxillary and sphenoidal sinusitis and nasal polyps in a patient with EGPA diagnosed after she presented some vasculitis manifestations (lung infiltrates and nodules with eosinophilic vasculitis on lung biopsy).



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