European Journal of Internal Medicine 128 (2024) 45–52

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

Red flags for clinical suspicion of eosinophilic granulomatosis with polyangiitis (EGPA)

R. Solans-Laqué [a,1], I. Rúa-Figueroa [b,1], M. Blanco Aparicio [c], I. García Moguel [d], R. Blanco [e], F. Pérez Grimaldi [f], A. Noblejas Mozo [g], M. Labrador Horrillo [b], J.M. Álvaro-Gracia [h], C. Domingo Ribas [i], G. Espigol-Frigolé [j], F. Sánchez-Toril López [k], F.M. Ortiz Sanjuán [l], E. Arismendi [m], M.C. Cid [j,*]

[a] Internal Medicine Department, H. Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain
[b] Rheumatology Department, Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Spain
[c] Pneumology Department, Hospital Universitario de A Coruña, Spain
[d] Allergy Department, Hospital Universitario 12 de Octubre; Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), Madrid, Spain
[e] Rheumatology Department, Hospital Universitario Marqués Valdecilla, IDIVAL, Immunopathology group, Santander, Spain
[f] Pneumology Department, H. Universitario de Jerez, Cádiz, Spain
[g] Internal Medicine Department, Hospital Universitario La Paz, Madrid, Spain
[h] Rheumatology Department, Hospital Universitario Gregorio Marañón, IisGM, Madrid, Spain
[i] Pneumology Department, Corporació Sanitaria Parc Taulí, Universitat Autònoma de Barcelona (UAB), Barcelona, Spain
[j] Autoimmune Diseases Department, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (FRCB-IDIBAPS), University of Barcelona, Barcelona, Spain
[k] Pneumology Department, Hospital Arnau Vilanova, Valencia, Spain
[l] Rheumatology Department, Hospital Universitario y Politécnico La Fe, Valencia, Spain
[m] Pneumology Department, Hospital Clínic de Barcelona, Universitat de Barcelona, Spain and CIBERES, Barcelona, Spain

ARTICLE INFO

Keywords:
Eosinophilic granulomatosis with polyangiitis
EGPA
Churg-Strauss
Clinical suspicion
Checklist
Eosinophilia
Recommendations
Asthma
Vasculitis

ABSTRACT

Background: Eosinophilic granulomatosis with polyangiitis (EGPA), is a rare ANCA-associated systemic vasculitis. Its overlapping features with other vasculitic or eosinophilic diseases, and the wide and heterogeneous range of clinical manifestations, often result in a delay to diagnosis.

Objective: To identify red flags that raise a suspicion of EGPA to prompt diagnostic testing and to present an evidence-based clinical checklist tool for use in routine clinical practice.

Methods: Systematic literature review and expert consensus to identify a list of red flags based on clinical judgement. GRADE applied to generate a strength of recommendation for each red flag and to develop a checklist tool.

Results: 86 studies were included. 40 red flags were identified as relevant to raise a suspicion of EGPA and assessed by the experts as being clinically significant. Experts agreed that a diagnosis of EGPA should be considered in a patient aged ≥6 years with a blood eosinophil level >1000 cells/μL if untreated and >500 cells/μL if previously treated with any medication likely to have altered the blood eosinophil count. The presence of asthma and/or nasal polyposis should reinforce a suspicion of EGPA. Red flags of asthma, lung infiltrates, pericarditis, cardiomyopathy, polyneuropathy, biopsy with inflammatory eosinophilic infiltrates, palpable purpura, digital ischaemia and ANCA positivity, usually anti-myeloperoxidase, among others, were identified.

Conclusion: The identification of a comprehensive set of red flags could be used to raise a suspicion of EGPA in patients with eosinophilia, providing clinicians with an evidence-based checklist tool that can be integrated into their practice.

* Corresponding author.
E-mail address: mccid@clinic.cat (M.C. Cid).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.ejim.2024.06.008
Received 2 October 2023; Received in revised form 31 May 2024; Accepted 7 June 2024
Available online 15 June 2024

1. Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome [1], is a systemic vasculitis classified as an anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) [1–3]. EGPA is a rare disease with an annual global incidence rate of 1.7 cases per million people per year and a prevalence of 15.6 cases per million people [4]. It arises during the 4th to 6th decade of life, with an average age at diagnosis of 49 years, although paediatric cases have also been reported. There is no sex predominance and no general apparent familial or geographical association [2], although some isolated familial cases have been described [5]. Survival rates for individuals diagnosed with EGPA exceed 96 % at 5 years [2]. However, patients experience frequent symptomatic flares and accumulate organ damage. EGPA is associated with high healthcare resource utilization, including inpatient admissions and emergency department visits, and is associated with an impaired quality of life (QoL) [6,7].

EGPA is a heterogeneous disease that affects multiple organs and can present with a variety of clinical manifestations, frequently non-specific, that often overlap with other pathologies. The typical presentation includes upper and lower respiratory tract involvement, peripheral neuropathy, cardiac involvement, and skin lesions. ANCA are positive (usually against myeloperoxidase [MPO]) in 30–35 % of cases, and more often in patients with clear clinical manifestations secondary to small vessel vasculitis [8,9]. In contrast, cardiac involvement is more frequent in ANCA-negative patients. The pathogenesis of EGPA remains unclear. Eosinophilia is a feature that differentiates EGPA from other ANCA-associated vasculitides and at the same time, is responsible for multiple clinical manifestations of the disease [2,10–12]. Eosinophilic manifestations include asthma, which is often persistent and/or severe; chronic rhinosinusitis with nasal polyposis; pulmonary infiltrates; gastrointestinal infiltration; infiltrative cardiomyopathy, and eosinophilia in peripheral blood and tissues. Vasculitic manifestations of EGPA include multiple mononeuritis, polyneuropathy, glomerulonephritis, purpura and rarely digital ischemia, and abdominal ischaemia [2,12]. Eosinophilic and vasculitic manifestations are often intermingled since eosinophils may be a component of vascular and perivascular infiltrates and a complete distinction between eosinophilic and vasculitis manifestations cannot be always established. For instance, neuropathy may have a vasculitic origin and/or an eosinophil-derived neurotoxicity component [13], and renal involvement may include necrotizing glomerulonephritis and/or eosinophilic-rich interstitial inflammation. ANCA, a biomarker more frequently associated with the presence of vasculitis, may be positive in patients with no typical vasculitis manifestations [12,14,15]. This heterogeneity and the wide range of clinical manifestations often result in a significant delay in diagnosis, with delays typically ranging from 3 to 9 years from the onset of asthma to the diagnosis of vasculitis [16]. It should be noted that the majority of patients with asthma and eosinophilia would never develop EGPA. Only a subgroup of them, faced with certain environmental stimuli, and probably with a predisposing genetic basis, will develop EGPA. Being able to identify warning signs and symptoms (“red flags”) that allow us to identify these patients early is a real challenge.

The diagnosis of EGPA is often challenging due to its rarity, heterogeneous and multiorgan clinical presentation, and overlap with other vasculitic or eosinophilic disorders. There are no commonly agreed diagnostic criteria for EGPA. Only different classification criteria are available, and the definitive diagnosis of EGPA is based on histological confirmation through biopsy of an affected organ or tissue, which demonstrates the presence of medium-small vessel vasculitis with eosinophilia. Therefore, a diagnosis of EGPA may be easily established in patients with asthma and eosinophilia with vasculitis, based on histology showing tissue eosinophilia, necrotizing vasculitis, and extravascular eosinophilic granulomas, as key histological features [8,12]. However, not all patients have confirmatory biopsies, and all disease definition components are not easily detectable. There have been different classification criteria for EGPA, since the 1990 American College of Rheumatology (ACR) classification criteria that identified six clinical or histological items (asthma, eosinophilia, neuropathy, non-fixed lung infiltrates, paranasal sinus involvement, and histological evidence of extravascular eosinophils) [17,18], to the 1993 and 2012 Chapel Hill Consensus’ Conference definitions and nomenclature that focused on histopathology findings [19,20], and more recently, the 2022 ACR/EULAR (European Alliance of Rheumatology Associations) classification [17]. In the later classification, a score of six or more across the following criteria is required to support the classification of a patient with vasculitis as having EGPA: obstructive pulmonary disease (score 3); nasal polyps (score 3); multiple mononeuritis (score 1); blood eosinophil count $>1 \times 109$/L (score 5); extravascular inflammation with predominance of eosinophils on biopsy (score 2); test positive for c-ANCA or anti-PR3 (reduce score by 3); haematuria (reduce score by 1). However, classification criteria should not be used as diagnostic criteria, as stated in the recently published evidence-based guideline for the diagnosis and management of EGPA [12]. Given the challenges to achieve a timely diagnosis for this rare and heterogenous condition, there is a need to define a comprehensive list of signs, symptoms, and laboratory parameters, that can be used to raise a suspicion of EGPA, as a first step in the diagnostic/classification process.

Here we report the results of a systematic literature review and expert consensus, undertaken to identify red flags for raising suspicion for EGPA, which should prompt clinicians to initiate a diagnostic process to confirm or refute an EGPA diagnosis. We also present an evidence-based clinical checklist tool for use in routine clinical practice to facilitate the identification of patients for whom EGPA should be suspected and further expert diagnostic evaluations should be undertaken.

2. Material and methods

2.1. Systematic literature review

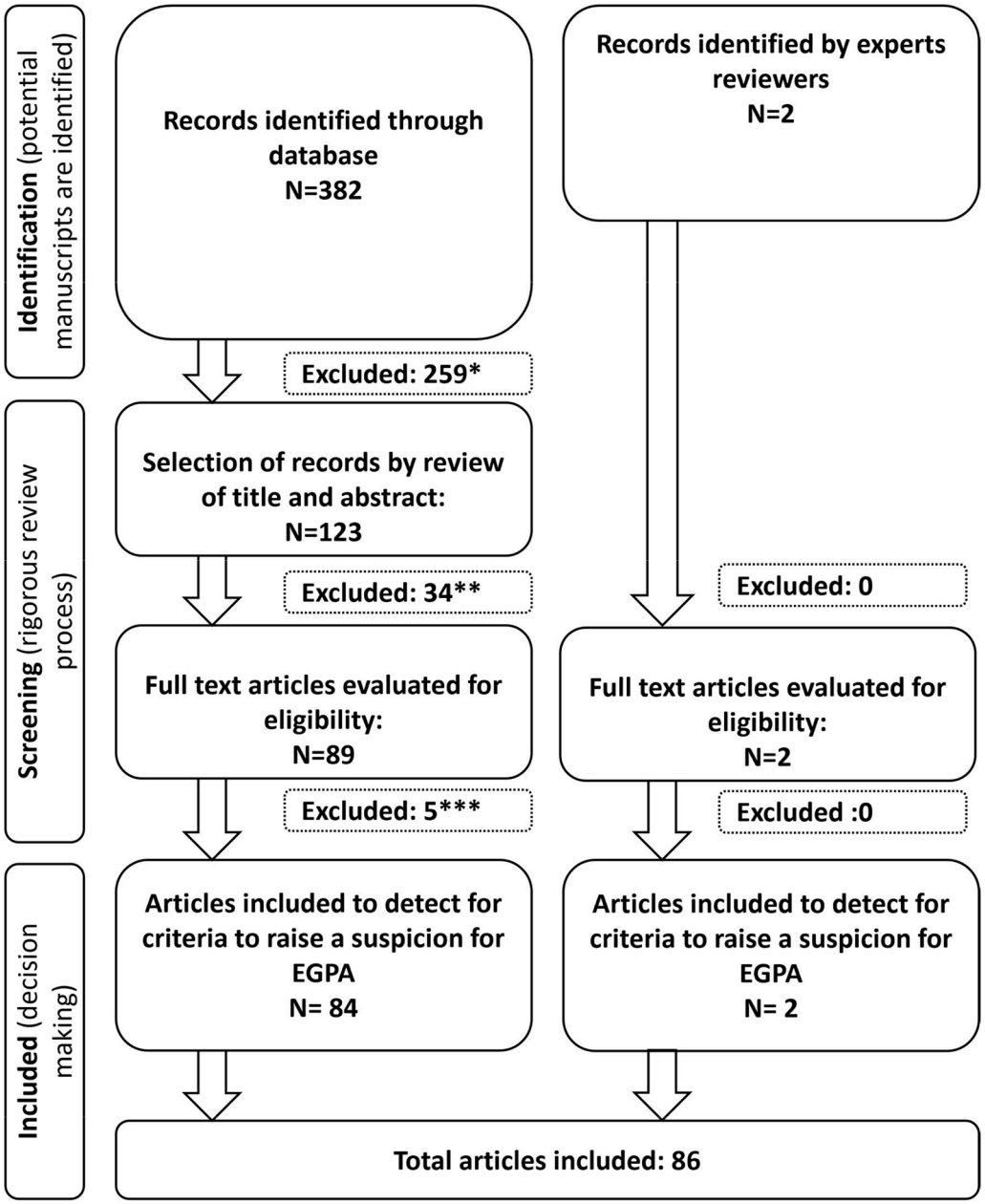
In accordance with evidence-based medicine standards, Patient-Intervention-Comparator-Outcome (PICO) criteria were developed in order to formulate an unbiased and effective literature search strategy to identify the most robust evidence with regards to the clinical question “*Which signs and symptoms should make the specialist physician suspect a possible case of EGPA in the population older than 6 years of age?*” The target population (P) was defined as patients over 6 years of age with a diagnosis of EGPA, and the intervention (I) was defined as the presence of symptoms, signs or laboratory parameters that contributed to a suspicion of EGPA. As this was not a treatment-focused review, no comparator (C) was included, and the outcome (O) was defined as a clinical suspicion of EGPA. With these parameters in place, the literature search was designed to capture original studies and case series that described symptoms, signs, or laboratory parameters present at the onset of the disease, before reaching the diagnosis of EGPA.

The literature search was conducted in the PubMed and Cochrane databases between January 1st, 1976 and September 20th, 2022 (the date on which the search was conducted) and was restricted to journal publications in English or Spanish for which an abstract was available. Search terms were defined as: (egpa OR "churg strauss") AND (debut OR "initial symptom" OR present OR criteria OR diagnosis OR classification) AND ("clinical course" OR "long-term" OR cohort) AND (("1976/1/1″ [Date - Publication]: "3000″[Date - Publication])) NOT (treatment [title]). Meta-analyses and reviews reporting case series already published in original articles were excluded, as were studies that did not assess any aspect related to EGPA or suspicion signals.

The titles and abstracts of all identified studies were independently screened by two reviewers for relevance and duplicates were removed. Disagreements in study selection between the two lead reviewers were resolved by a third reviewer. From all studies that met the inclusion/exclusion criteria, signs for clinical suspicion of EGPA were extracted and classified according to the organ/system affected.

2.2. Expert consensus

A multidisciplinary nominal group consensus approach was employed for expert consensus generation. The specialties involved (respiratory medicine, allergic medicine, rheumatology, and internal medicine [specifically those more commonly treating patients with EGPA]) cover the vast majority of the multiple clinical manifestations of EGPA. The process consisted of a face-to-face meeting during which the clinical signals extracted from the literature review were evaluated. Three working groups were established. The information available to each group comprised the clinical signals together, the frequency with which they appeared in the literature and the type of study from which they were extracted. The clinical manifestations were grouped into the following categories: autoimmune markers; blood markers; dermatological, gastrointestinal, pulmonary, otorhinolaryngological, renal, ophthalmological, cardiovascular, neurological, and musculoskeletal involvement; as well as constitutional syndrome and general symptoms. Each working group reviewed signals and considered whether signals were sufficiently specific to raise suspicion for EGPA, whether related signals could be grouped, and whether signals were easy to understand and exploit in the clinical setting. Following the review of the evidence, the working groups employed clinical judgment (based on frequency



Reasons: *Focused on follow up, treatment or relapse n=48; Focused on other pathologies n=37; Focused on epidemiology n=27; EGPA diagnosis / no information about suspicion n=21; Out of scope / others n=126 | ** Out of scope: not focused on suspicion criteria of EGPA n=all

Fig. 1. PRISMA flowchart for the systematic literature review.

observed as experts and/or in the potential seriousness of leaving a possible manifestation untreated as EGPA) to classify signals as being of high, medium, low, or no relevance regarding a suspicion for EGPA.

After the face-to-face meeting, a list of red flags classed as of high, medium, or low relevance was compiled based on the evidential review (including the frequency with which they appeared in the literature and the type of study from which they were extracted) and the clinical judgment of the expert group. The ACR/EULAR criteria [21] were included in this list. The complete list of red flags was then reviewed by all experts via an online questionnaire and re-classified as being of high, medium, low, or no relevance, regarding a suspicion for EGPA, in addition to practical utility within a clinical setting. A total of 40 suspicion signals were confirmed and agreed upon by all experts during an on-site multidisciplinary nominal group consensus.

GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) methodology was used to assess the quality of the scientific evidence supporting each criterion included in the shortlist [22]. The strength of recommendation for each criterion was determined based on the definitions employed by the National Comprehensive Cancer Network (NCCN) [23] using a combination of the level of relevance concerning a suspicion for EGPA according to the expert opinion and the GRADE assessment (strength of evidence) (**Supplementary Table S2**):

- Category 1: The available evidence is of high quality (grade 1) and there is consensus among experts;
- Category 2A: The available evidence is of lower quality (grade 2) and there is unanimous consensus among experts;
- Category 2B: The available evidence is of lower quality (grade 2) and there is no unanimous consensus among experts;
- Category 3: The available evidence is of any grade, but there is no consensus among experts.

ANCA, anti-neutrophil cytoplasm antibody; BNP, B-type natriuretic protein; EGPA, Eosinophilic granulomatosis with polyangiitis; IgE, immunoglobulin E

Fig. 2. Clinical checklist tool of red flags for suspicion of EGPA.
• If a patient presents with the indicated levels of eosinophilia, the detection of any of the listed factors, with no other apparent cause, should alert to the possibility of EGPA.
• The presence of more than one factor will reinforce the suspicion of EGPA.

2.3. Development of a clinical checklist tool

Red flags identified as suspicion signals for EGPA were categorised by organ system, manifestation, and laboratory test to facilitate a rational, evidence-based clinical review of patients presenting with eosinophilia.

3. Results

A total of 382 records were identified and reviewed for inclusion, of which 86 studies were included in the literature review (Fig. 1, **Supplementary Table S1**). From the 86 publications considered eligible for full review and data extraction, a total of 40 red flags were identified as relevant to raise suspicion for EGPA (Fig. 2) and assessed by the experts as being of high, medium, or low relevance regarding a suspicion for EGPA (**Supplementary Table S2**). The red flags depicted in Fig. 2 are identified in accordance with the articles reviewed and categorized by experts into headings within the figure, indicating potential organ involvement.

The quality of scientific evidence and strength of recommendation was determined for each criterion (**Supplementary Table S2**). Since all signals were derived from observational studies, the GRADE level of evidence was classified as low. Experts agreed that a diagnosis of EGPA should be considered in a patient aged 6 years and over with a blood eosinophil level >1000 cells/μL if untreated and >500 cells/μL if previously treated with any medication likely to have altered the blood eosinophil count, and that other causes of hypereosinophilia need to be considered (parasites, paraneoplastic, drugs, previous diagnosis of hypereosinophilic syndrome etc.) [12,24–26]. The presence of asthma and/or nasal polyposis should reinforce a suspicion of EGPA above other eosinophilic disorders. The additional presence of any of the 40 red flags identified as relevant to raise suspicion for EGPA can be considered to reinforce the suspicion of EGPA.

Because of the rarity of the disease, involvement of various specialties, varying levels of expertise, and the subjective nature of grading, there was no unanimous consensus in grading. Consequently, all identified red flags hold relevant significance.

3.1. Respiratory red flags

Four respiratory red flags were considered by the experts as being of high relevance to raise suspicion for EGPA: asthma, lung infiltrates/nodule(s)/eosinophilic alveolitis, eosinophilic pleural effusion and alveolar hemorrhage/hemoptysis. In addition, chronic cough of over 8 weeks duration or wheezing (not explained by another cause) was considered to be of medium relevance.

3.2. Cardiac red flags

Three cardiac red flags were considered by the experts as being of high relevance to raise suspicion for EGPA: pericardial effusion/pericarditis, cardiomyopathy, and ischaemic heart disease/arterial occlusion/infarction in a patient without identified cardiovascular risk factors and without suspicion of other causes. In addition, cardiomegaly was considered to be of medium relevance, unless associated with the above manifestations.

3.3. Vascular red flags

One vascular red flag, digital ischemia, was considered by the experts as being of high relevance to raise suspicion for EGPA. In addition, venous thrombosis (without any other triggering factors) was considered to be of medium relevance.

3.4. Otorhinolaryngological red flags

One otorhinolaryngological red flag, nasal polyposis, usually associated with chronic rhinosinusitis, was considered by the experts as being of high relevance to raise suspicion for EGPA upfront of other eosinophilic diseases. In addition, chronic media otitis was considered to be of medium relevance.

3.5. Dermatological red flags

One dermatological red flag, palpable purpura, was considered by the experts as being of high relevance regarding raising suspicion for EGPA. In addition, the presence of skin lesions such as ulcers, urticaria, nodules, and papules, not explained by another cause, were considered to be of medium relevance.

3.6. Neurological red flags

Two neurological red flags, mononeuritis multiplex/polyneuropathy, and paraesthesia, were considered by the experts to be of high relevance for raising suspicion for EGPA. In addition, the presence of cerebrovascular disease (other pathologies ruled out) was considered to be of medium-high relevance.

3.7. Renal red flags

One renal red flag, glomerulonephritis, was considered by the experts as being of high relevance to raise suspicion for EGPA. Although not very frequent, it is virtually absent in other eosinophilic diseases and its potential severity makes it a relevant warning manifestation. In addition, the presence of glomerular extracapillary proliferation on renal biopsy or renal infarction was considered to be of medium relevance.

3.8. Gastrointestinal red flags

One gastrointestinal red flag, ischaemic injuries including intestinal ischemia (including recurrent abdominal pain that is ischaemic in nature (not explained by another cause) and perforation (gastric, oesophageal, and small intestine unexplained by any other cause), were considered by the experts to be of medium-high relevance to raise suspicion for EGPA, although the experts' experience was very asymmetric. In addition, the presence of chronic diarrhoea and melena (not explained by another cause) were considered to be of medium relevance.

3.9. Musculoskeletal red flags

Two musculoskeletal red flags, myositis/myopathy, and polyarthritis (with no alternative explanation), were considered by the experts to be of medium relevance in raising suspicion for EGPA.

3.10. Ophthalmological red flags

Two ophthalmological red flags, retinal vasculitis, and episcleritis/scleritis, were considered by the experts to be of medium relevance regarding raising a suspicion for EGPA. In addition, the presence of orbital inflammatory disease/orbital pseudotumor and red eyes (conjunctivitis and keratitis), were considered to be of medium relevance.

3.11. General red flags

The presence of constitutional syndrome and/or fever (not attributable to any other cause) was considered by the experts to be of high relevance for raising a suspicion of EGPA.

3.12. Histopathological red flags

Biopsy with inflammatory infiltrate predominantly eosinophilic, and vasculitis on biopsy, were considered by the experts as being of high relevance regarding raising suspicion for EGPA.

3.13. Analytical marker-related red flags

ANCA positivity, particularly with anti-MPO specificity, was considered by the experts to be of high relevance for raising suspicion of EGPA. It is important to remark that anti-PR3 specificity is much less frequent in EGPA but its presence should not deter from suspecting EGPA in the setting of significant eosinophilia, since in 5–10 % of patients with ANCA-positive EGPA, ANCA have anti-PR3 specificity [27–29]. In addition, elevated creatinine (together with sediment alteration), and proteinuria (>500 mg/24 h) were considered to be of medium relevance, and elevated troponin (that cannot be explained by another cause), high B-type natriuretic peptide (BNP) without any other apparent cause, high immunoglobulin E, and positive rheumatoid factor were considered to be of low relevance.

3.14. Clinical checklist tool for suspicion of EGPA in a patient presenting with eosinophilia

Fig. 2 displays a clinical checklist tool suitable for use in routine practice for the evaluation of a patient aged 6 years and over with a blood eosinophil level >1000 cells/μL if untreated and >500 cells/μL if previously treated with any medication likely to have altered the blood eosinophil count. Red flags considered to raise a suspicion of EGPA are grouped by organ system, manifestations, and laboratory test.

4. Discussion

The current systematic literature review and multidisciplinary expert consensus has, for the first time, enabled the identification of evidence-based red flags that can be used to raise a suspicion for EGPA in clinical practice. The red flags identified are relevant for patients older than 6 years of age with blood eosinophil levels of >1000 cells/μl (blood eosinophil count $>1 \times 10^9$/L), with no pharmacological treatment that could explain an alteration of this value, or levels of > 500 cells /μL with a treatment that could decrease this value (such as glucocorticoids).

The insights gained via a systematic approach to evidence generation, expert consensus rating and GRADE methodology have enabled the consolidation of a comprehensive list of red flags applicable to the clinical context of this rare, multisystem, multiorgan disease. One recently published multidisciplinary guideline for the diagnosis and treatment of EGPA provide one recommendation ("statement 1″) focused on settings where EGPA should be considered. However, in contrast with our proposal, that statement doesn't comprise an exhaustive list of red flags, exposed in a systematic way.

EGPA is considered to be a subtype of ANCA-associated vasculitis and classification of EGPA can only be achieved in patients with vasculitis (histologically demonstrated or with strong clinical surrogates, including mononeuritis multiplex, purpura, glomerulonephritis or intestinal ischemia) [8]. Current ACR/EULAR classification criteria are useful for the differential diagnosis compared with other small vessel vasculitides and are stringent to achieve maximum sensitivity and specificity. However, EGPA may present with broad clinical manifestations, some of which are transient and non-specific, and the presentation and progression of the disease can differ markedly between individual patients, without a consistent pattern of indicators that EGPA may be the underlying pathology [1–3,10,11]. Unusual combinations of features of this rare disease can contribute to a significant delay in diagnosis [16]. The identification of a wider set of signs and symptoms of suspicion (red flags) that are less specific could contribute to an earlier diagnosis of the disease by prompting a thorough investigation of subtle manifestations with appropriate tests, avoiding diagnostic delay and therefore, hypothetically, slowing down the progression of the disease. Thanks to the availability of new potentially disease-modifying treatments for EGPA, achieving diagnosis early in the course of the disease is critical to improve outcomes for patients with this condition [30–37].

We identified 40 red flags of high, medium, and low relevance regarding suspicion of EGPA in patients aged 6 years and over presenting with eosinophilia. The presence of a single red flag does not necessarily support a strong suspicion of EGPA or justify a detailed investigation, but it does indicate that EGPA should be considered. The type and number of tests will be guided by clinical judgment and specialist consultation when necessary. In contrast, the presence of multiple red flags in an individual patient may reinforce the suspicion of EGPA. The experts note that if the red flags identified comprise asthma and/or nasal polyposis, the level of suspicion of EGPA increases as compared with other eosinophilic diseases. However, these manifestations are very common and, in the absence of any indication of systemic involvement, are insufficient to make the diagnosis.

The evidence-based clinical checklist tool developed derived from the systematic literature review and expert consensus is suitable for use in routine clinical practice to achieve the rapid identification of patients for whom a suspicion of EGPA warrants additional investigation. The development of a clinical checklist tool was regarded by the experts as an essential step to enable the translation of the insights generated into clinical practice. Checklists are a widely used cognitive tool to rationalize and standardize complex decision-making and to ensure that all relevant parameters – in this case, red flags – are considered [38]. They are increasingly used in diverse medical settings, in particular to improve patient safety [39–41]. Grouping of red flags by organ system, manifestations, and laboratory tests, enables clinicians to systematically consider all potential red flags that may raise a suspicion for EGPA.

Potential limitations of the current evaluation relate to the heterogeneity and lack of systematic evaluation of the clinical manifestations of EGPA. In particular, red flags were mainly drawn from case studies and a small number of retrospective analyses. Furthermore, for the current evaluation, each putative red flag was defined, and its relevance was assessed independently from all other signals. Compelling evidence would have resulted from prospective follow-up studies performed in patients with asthma or eosinophilia to determine the percentage of patients developing EGPA and their potential distinctive features but such studies do not exist.

Moreover, since EGPA is a rare disease, expert experience is necessarily limited and opinion may be biased by the frequency with which individual experts have observed particular red flags. Even infrequent, some items were graded as high given the potential deleterious consequences of leaving these untreated. A potential area for future research might be to evaluate other clinical manifestations not yet published in the literature, or interactions between the identified red flags, for example using a cluster analysis methodology. Progress in biomarkers useful for discrimination between eosinophilic conditions would be welcome. Regardless, we were able to identify a coherent set of red flags and develop a clinical checklist tool for use in clinical practice that can be used to evaluate patients, raise suspicion for EGPA, and prompt further investigation.

5. Conclusions

Systematic literature review, multidisciplinary expert consensus rating, and GRADE methodology have enabled, for the first time, the identification of a comprehensive set of 40 red flags that may be used to raise suspicion for EGPA in patients with eosinophilia, providing clinicians with an evidence-based checklist tool that can be integrated into their routine practice.

Declaration of competing interest

Iñigo Rúa-Figueroa: Lectures and advisors boards for GSK. No other conflicts of interest.

Roser Solans Laqué: Honoraria for consultancy and conferences from GSK, and conferences from CSL- Vifor.

Marina Blanco Aparicio declares to have received payment or honoraria for lectures, presentations, speakers' bureaus, or educational events and support for attending meetings and/or travel for AstraZeneca, GSK, Sanofi, Chiesi, TEVA and Faes.

Ismael García Moguel: Consultant and speaker: Novartis, AstraZeneca, Teva, Novartis, GSK, Sanofi Genzyme, Chiesi, Allergy therapeutics, Leti, Stallergenes, ALK-Abelló, Mundipharma, Pfizer, and Orion Pharma. PI clinical trials: Novartis, GSK, AstraZeneca, Sanofi Genzyme.

Ricardo Blanco: Grants/research support from AbbVie, MSD, and Roche, and had consultation fees/participation in a company-sponsored speaker's bureau from AbbVie, Pfizer, Roche, Lilly, UCB, Bristol-Myers, GSK, Janssen, Novartis and MSD.

Francisco Pérez Grimaldi: Honoraria for conferences from AstraZeneca, GSK, Sanofi, Novartis, Chiesi, Teva, Esteve, Menarini y Boehringer-Ingelheim.

Ana Noblejas Mozo: Colaboration with CSL Vifor, Gebro Pharma, Astra Zeneca. Colaboration in a vasculitis meeting with patients: CSL Vifor. Honoraria for consultancy from GSK.

Moises Labrador Horrillo: Payment for lectures including service on speakers' bureaus from: AstraZeneca, GSK, Novartis and Sanofi. Consultancy from: AstraZeneca, Novartis and GSK.

J.M. Álvaro-Gracia: Honoraria for lecturing, advisories and Congress attendance from AbbVie, AstraZeneca, Galapagos, Gilead, Pfizer, Novartis, GSK, Lilly, MSD y UCB.

Christian Domingo Ribas. CDR has acted as consultant for GSK, AstraZeneca and Sanofi and has received funding for travel or speaker fees from ALK, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Menarini, MSD, Novartis, Stallergenes and Pfizer.

Georgina Espígol-Frigolé: Honoraria for consultancy from Janssen, GSK and CSL-Vifor. Congress attendance from Boehringer-Ingelheim.

Fernando Sánchez Toril. I have received personal fees (payments for presentations, advisory boards, etc.) from: ALK, AstraZeneca, Bial, Boehringer Ingelheim, Chiesi, FAES, Gebro Pharma, GSK, Menarini, Novartis, Pfeizer, TEVA and Sanofi. I have participated in clinical trials and received research grants from: AstraZeneca, Chiesi, GSK, Novartis, TEVA, Sanofi. I am not employed (including part-time) in any pharmaceutical industry. I do not maintain any relationship with the tobacco industry.

Francisco Ortiz Sanjuán: Advisor, Review Panel member or Consultant fee from GSK, Grünenthal and received financial aid for attendance at medical conferences from Lilly.

Ebymar Arismendi: Honoraria for consultancy, advisory board and/or conferences from GSK, AstraZeneca, MSD, Novartis, Chiesi, Gebro Pharma and Sanofi-Genzyme.

Maria C Cid: Consulting fees from GSK, AbbVie, CSL- Vifor and AstraZeneca; royalties from UpToDate, and a research grant from Kiniksa Pharmaceuticals Corp.

Funding source

The present work was funded by GSK. Authors were in full editorial control of the content and conclusions and accepted full responsibility for the final approval of the manuscript. The decision to submit for publication was taken solely by the authors and the sponsor did not place any restrictions on access to the data or on the statements made in the manuscript.

GSK funded Adelphi Targis who undertook the literature research and provided medical writing support under the direction and guidance of the expert authors. The authors were solely responsible for critical assessment and interpretation of results of the literature review and approved the final content.

Acknowledgements

We would like to acknowledge GlaxoSmithKline (GSK) employee - Beatriz Velasco-Laorga for her support in carrying out this project. GSK provided funding and reviewed a draft of the publication for data accuracy only, but the final and published content is the authors' sole work.

Finally, we would like to thank Adelphi Targis, for its support in implementing the project.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2024.06.008.

References

[1] Churg J, Strauss L. Allergic granulomatosis, allergic angiitis, and periarteritis nodosa. Am J Pathol 1951;27:277–301.
[2] White J, Dubey S. Eosinophilic granulomatosis with polyangiitis: a review. Autoimmun Rev 2023;22:103219.
[3] Furuta S, Iwamoto T, Nakajima H. Update on eosinophilic granulomatosis with polyangiitis. Allergol Int 2019;68:430–6.
[4] Redondo-Rodriguez R, Mena-Vázquez N, Cabezas-Lucena AM, Manrique-Arija S, Mucientes A, Fernández-Nebro A. Systematic review and metaanalysis of worldwide incidence and prevalence of Antineutrophil Cytoplasmic Antibody (ANCA) associated vasculitis. J Clin Med 2022;11:2573.
[5] Alyasin S;, Khoshkhui M, Amin R. Familial Churg-Strauss syndrome in a sister and brother. Iran J Allergy Asthma Immunol 2015;14:338–40.
[6] Benarous L, Terrier B, Laborde-Casterot H, et al. Employment, work disability and quality of life in patients with ANCA-associated vasculitides. The EXPOVAS study. Clin Exp Rheumatol 2017;35(Suppl 103):40–6.
[7] Jakes RW, Kwon N, Nordstrom B, Goulding R, Fahrbach K, Tarpey J, Van Dyke MK. Burden of illness associated with eosinophilic granulomatosis with polyangiitis: a systematic literature review and meta-analysis. Clin Rheumatol 2021;40:4829–36.
[8] Moiseev S, Bossuyt X, Arimura Y, et al. International consensus on antineutrophil cytoplasm antibodies testing in eosinophilic granulomatosis with polyangiitis. Am J Respir Crit Care Med 2020;202:1360–72.
[9] Cohen Tervaert JW, Limburg PC, Elema JD, Huitema MG, Horst G, The TH, Kallenberg CGM. Detection of autoantibodies against myeloid lysosomal enzymes: a useful adjunct to classification of patients with biopsy-proven necrotizing arteritis. Am J Med 1991;91:59–66.
[10] Janson C, Bjermer L, Lehtimäki L, et al. Eosinophilic airway diseases: basic science, clinical manifestations and future challenges. Eur Clin Respir J 2022. https://doi.org/10.1080/20018525.2022.2040707.
[11] Ríos-Garcés R, Prieto-González S, Hernández-Rodríguez J, Arismendi E, Alobid I, Penatti AE, Cid MC, Espígol-Frigolé G. Response to mepolizumab according to disease manifestations in patients with eosinophilic granulomatosis with polyangiitis. Eur J Intern Med 2022;95:61–6.
[12] Emmi G, Bettiol A, Gelain E, et al. Evidence-Based Guideline for the diagnosis and management of eosinophilic granulomatosis with polyangiitis. Nat Rev Rheumatol 2023;19:378–93.
[13] Nishi R, Koike H, Ohyama K, Fukami Y, Ikeda S, Kawagashira Y, Iijima M, Katsuno M, Sobue G. Differential clinicopathologic features of EGPA-associated neuropathy with and without ANCA. Neurology 2020. https://doi.org/10.1212/WNL.0000000000009309.
[14] Sinico RA, Di Toma L, Maggiore U, et al. Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome. Arthritis Rheum 2005;52:2926–35.
[15] Sablé-Fourtassou R, Cohen P, Mahr A, et al. Antineutrophil cytoplasmic antibodies and the churg–strauss syndrome. Ann Intern Med 2005;143:632.
[16] Baldini C, Talarico R, Della Rossa A, Bombardieri S. Clinical manifestations and treatment of churg-strauss syndrome. Rheumatic Dis Clinics North Am 2010;36:527–43.
[17] Grayson PC, Ponte C, Suppiah R, et al. 2022 American College of rheumatology/European alliance of associations for rheumatology classification criteria for eosinophilic granulomatosis with polyangiitis. Arthritis Rheumatol 2022;74:386–92.
[18] Masi AT, Hunder GG, Lie JT, et al. The American College of Rheumatology 1990 criteria for the classification of churg-strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum 1990;33:1094–100.
[19] Bielsa I. Update of systemic vasculitides nomenclature. International chapel hill consensus conference, 2012. Actas Dermosifiliogr 2015;106:605–8.
[20] Fries J.F., Hunder G.G., Bloch D.A., et al. (1990) The American college of rheumatology 1990 criteria for the classification of vasculitis summary.
[21] Grayson PC, Ponte C, Suppiah R, Robson JC, Craven A, Judge A, et al. 2022 American college of rheumatology/european alliance of associations for

rheumatology classification criteria for eosinophilic granulomatosis with polyangiitis. Ann Rheum Dis 2022;81:309–14.
[22] Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490.
[23] Poonacha TK, Go RS. Level of scientific evidence underlying recommendations arising from the national comprehensive cancer network clinical practice guidelines. J Clinic Oncol 2011;29:186–91.
[24] Shomali W, Gotlib J. World Health Organization-defined eosinophilic disorders: 2022 update on diagnosis, risk stratification, and management. Am J Hematol 2022;97:129–48.
[25] Leverone N, Tran S, Barry J, Akuthota P. Diagnoses associated with peripheral blood eosinophilia. Ann Allergy Asthma Immunol 2021;127:597–8.
[26] Khoury P., Akuthota P., Kwon N., Steinfeld J., Roufosse F (2023) HES and EGPA. Mayo Clin Proc 98:1054–1070.
[27] Solans-Laqué R, Fraile G, Rodriguez-Carballeira M, et al. Clinical characteristics and outcome of Spanish patients with ANCA-associated vasculitides Impact of the vasculitis type, ANCA specificity, and treatment on mortality and morbidity. Medicine (Baltimore) 2017. https://doi.org/10.1097/MD.0000000000006083.
[28] Rubenstein E, Maldini C, Vaglio A, et al. Cluster analysis to explore clinical subphenotypes of eosinophilic granulomatosis with polyangiitis. J Rheumatol 2023;50:1446–53.
[29] Papo M, Sinico RA, Teixeira V, et al. Significance of PR3-ANCA positivity in eosinophilic granulomatosis with polyangiitis (Churg-Strauss). Rheumatology (Oxford) 2021;60:4355–60.
[30] Manka LA, Guntur VP, Denson JL, Dunn RM, Dollin YT, Strand MJ, Wechsler ME. Efficacy and safety of reslizumab in the treatment of eosinophilic granulomatosis with polyangiitis. Ann Allergy Asthma Immunol 2021;126:696–701. e1.
[31] Martínez-Rivera C, Garcia-Olivé I, Urrutia-Royo B, Basagaña-Torrento M, Rosell A, Abad J. Rapid effect of benralizumab in exacerbation of severe eosinophilic asthma associated with eosinophilic granulomatosis with polyangiitis. BMC Pulm Med 2021;21:35.
[32] Coppola A, Flores KR, De Filippis F. Rapid onset of effect of benralizumab on respiratory symptoms in a patient with eosinophilic granulomatosis with polyangiitis. Respir Med Case Rep 2020;30:101050.
[33] Nanzer AM, Dhariwal J, Kavanagh J, et al. Steroid-sparing effects of benralizumab in patients with eosinophilic granulomatosis with polyangiitis. ERJ Open Res 2020; 6:00451–2020.
[34] Guntur VP, Manka LA, Denson JL, Dunn RM, Dollin YT, Gill M, Kolakowski C, Strand MJ, Wechsler ME. Benralizumab as a steroid-sparing treatment option in eosinophilic granulomatosis with polyangiitis. J Allergy Clin Immunol Pract 2021; 9:1186–93. e1.
[35] Padoan R, Chieco Bianchi F, Marchi MR, Cazzador D, Felicetti M, Emanuelli E, Vianello A, Nicolai P, Doria A, Schiavon F. Benralizumab as a glucocorticoid-sparing treatment option for severe asthma in eosinophilic granulomatosis with polyangiitis. J Allergy Clin Immunol Pract 2020;8:3225–7. e2.
[36] Takenaka K, Minami T, Yoshihashi Y, Hirata S, Kimura Y, Kono H. Decrease in MPO-ANCA after administration of benralizumab in eosinophilic granulomatosis with polyangiitis. Allergol Int 2019;68:539–40.
[37] European Medicines Agency (EMA) (2022) Nucala(R). INN-mepolizumab. Summary of Product Characteristics. . https://www.ema.europa.eu/en/medicines/human/EPAR/nucala. Accessed 12 Dec 2023.
[38] Hales B, Terblanche M, Fowler R, Sibbald W. Development of medical checklists for improved quality of patient care. Int J Qual Health Care 2007;20:22–30.
[39] Dubois H, Schmidt PT, Creutzfeldt J, Bergenmar M. Person-centered endoscopy safety checklist: development, implementation, and evaluation. World J Gastroenterol 2017;23:8605–14.
[40] Ko HC, Turner TJ, Finnigan MA. Systematic review of safety checklists for use by medical care teams in acute hospital settings - limited evidence of effectiveness. BMC Health Serv Res 2011;11:211.
[41] World Health Organization (2009) WHO Guidelines for Safe Surgery 2009: Safe Surgery Saves Lives.