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Short Communication

Too early diagnosis of granulomatosis with polyangiitis (GPA) in the first month of initial presentation

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Abstract

Granulomatosis with Polyangiitis (GPA) is a systemic small sized vascular disease involving vasculitis, granuloma, and necrosis that most often targets the Ear, Nose and Throat (ENT) and/or Lungs and/or Kidneys, and it is classically associated with Anti-Neutrophil Cytoplasmic Antibody (ANCA) positivity. The initial presentations of GPA most often indicate ENT involvement, possibly lungs involvement, and occasionally kidneys involvement. Nowadays the GPA can be divided into two types include Limited GPA: (ENT± Lung) involvement and Systemic GPA: [(ENT± Lung) + Kidney] involvement. ANCA is positive in 90% of the cases with active systemic GPA whereas, it is positive in about 60% of the cases with limited GPA and mainly is C-ANCA/anti-PR3. We need to know that early diagnosis of GPA and subsequent rapid initiation of treatment; may completely cure the disease. Well-known Criteria have been presented for Classifying/Diagnosing Wegener's Granulomatosis or GPA that are: "The 1990 American College of Rheumatology (ACR) Classification Criteria for Wegener's Granulomatosis", "The 2007 European Medicine Agency Algorithm (EMA) Diagnostic Criteria for Systemic GPA", and "The ACR/European League Against Rheumatism (EULAR) Provisional 2017 Classification Criteria for GPA". But they are mainly for classifying GPA and none have sufficient sensitivity and specificity for early diagnosis. Whereas, here are two Criteria, which have been designed by the corresponding author of this article that are "The Iran Criteria for Early Diagnosis of GPA", and "The 2017 ACR/EMA Revised Criteria for Too Early Diagnosis of GPA". It is claimed that they are able to diagnose GPA in the first a few months and the first month of the disease, respectively.

Keywords: GPA; ANCA; ACR criteria; EMA criteria; ACR/EULAR criteria; Iran criteria; ACR/EMA criteria

Introduction

Granulomatosis with Polyangiitis is a systemic small sized vascular disease involving vasculitis, granulomatous inflammation, and necrosis that most often targets the ENT and/or Lungs and/or Kidneys, and it is classically associated with Anti-Neutrophil Cytoplasmic Antibody (ANCA) positivity [1,2]. It was previously termed as Wegener's granulomatosis, which was changed to Granulomatosis with Polyangiitis in January 2011 with the abbreviation GPA [3]. The prevalence of GPA in the world varies from 2 in 100,000 to 5 in 100,000, which according to the author of this article, the prevalence of 3 in 100,000, and annual incidence of 1 in 100,000 are the best options [4]. Although this disease can affect people of any age, the typical age for onset is between 40 and 60 years, with an average age of 45 years. GPA affects both genders, but men are slightly more likely than women to have the disease, with 55.9% of men and the rest women [5]. GPA is uncommon in children, but it is not uncommon in old age, especially over the age of 70. Less than 15 percent of GPA patients were previously thought to be children (age <18), but today it is thought to be less than 5 percent [6]. Although GPA can affect people of any race and skin color in any geography, it is found in the vast majority of cases (>90%) in whites [7]. We need to know that early diagnosis of GPA and subsequent rapid initiation of treatment; may completely cure the disease. Currently, the interval between the onset of GPA and its definitive diagnosis is between 2 and 20 months [8]. In this article attempts are made to present too early diagnosis of GPA in the first month of the disease.

Methods

Study protocol

The study protocols were approved by the Medical Ethics Committee of Tehran University of Medical Sciences for two studies:

Study I: Extraction of "Amir-A' lam Hospital Recommendation for Early Detection of GPA in Sinusitis [6].

Study II: Extraction of "The Iran Criteria for Early Diagnosis of GPA" and determining its sensitivity and comparison with the sensitivity of the 1990 ACR Classification Criteria for Wegener's Granulomatosis.

Both of the above studies have been performed in Amir-A'lam Hospital in Tehran. It is necessary to mention here that Amir-A' lam General Hospital is the Tertiary Referral Center for ENT patients in Iran.

In the first study, ten types of Atypical Sinusitis (AtS) were identified and collected by the author of this article (ISA), and the patients with AtS were compared to the patients with typical Sinusitis by a double-blind method and followed up for more than a year. Finally, applying the 1990 ACR Criteria, after one year of follow-up, I found that in the group of patients with AtS four times more than the control group, i.e. typical sinusitis, GPA is observed.

In the second study, my goal was to extract very sensitive Criteria for the diagnosis of GPA in its initial presentation. It is necessary to mention here that so all patients with incurable diseases of the nose, sinuses, and throat from all over the country were sent to Amir-A'lam Hospital, and I as the only Rheumatologist at the Hospital, gradually through Rheumatologic consultations found that a significant percentage of these patients have GPA. Ten years of consultation and follow-up with GPA patients and extensive study in this field have given me the insight to be able to design a native diagnostic Criteria for GPA. In this way, the medical records of the patients with a definite diagnosis of GPA, made by a single expert Rheumatologist (ISA) at the outpatient Rheumatology Clinic or Rheumatology Clinic of Amir-A´ lam Hospital between 2001 and 2011 were reviewed. Infectious disease specialists and ENT specialists helped in ruling out other suspected diagnoses when necessary. The patients with the overlapped diseases, suspected as MPA, on the treatment of GPA before referral to the clinic, follow-up for less than 1 month, and the patients with incomplete medical records were excluded. Demographic and clinical information including gender, age at diagnosis, disease duration, and follow-up duration were extracted. The findings of imaging (chest or sinus X-ray, CT-scan of sinuses, and HRCT of lungs) were interpreted by both an experienced Rheumatologist and a Radiologist. Serum ANCA was done by indirect immunofluorescence assay or were analyzed for specific antibodies directed against PR3 or MPO by enzyme-linked immunosorbent assay (ELISA). The data on each criterion of "The Iran Criteria for Early Diagnosis of GPA" and "The 1990 ACR Classification Criteria for Wegener's granulomatosis" were extracted and the patients with a definite diagnosis of GPA according to each set of Criteria were recognized. The Iran Criteria for Early Diagnosis of GPA suggests evaluation of three organs and two laboratory findings (ANCA and biopsy), after ruling out other prominent diagnoses by history and physical examination. The appropriate approach toward a correct diagnosis for a patient suspected as suffering from GPA is "Amir-A´ lam Hospital approach towards the diagnosis of GPA". Considering the clinical diagnosis of GPA by a Rheumatologist as the gold standard, the sensitivity of the two sets of Criteria was measured using the following formula: Sensitivity=(number of the patients classified as GPA by the Criteria)/(number of the patients diagnosed as GPA by an expert Rheumatologist). Statistical analysis was conducted using SPSS software version 16.00 (SPSS Inc., Chicago, IL). Continuous and categorical variables are expressed as the mean standard error of the mean (SEM) and number (%), respectively.

By shifting a score from the pathological criterion to the ENT criterion, a new Criteria was reproduced from Iran Criteria for GPA. The new Criteria were evaluated in the patient's file of the second study. In all of those patients, the GPA diagnosis was reaffirmed, but in all patients, the GPA diagnosis was available in the first month of the disease based on the new criteria. And this new Criteria; "The 2017 ACR/EMA Revised Criteria for Too Early Diagnosis of GPA" was named. In both of the above Criteria presented by me: I have imagined a specificity of over 90%. The reason behind this level of specificity for the above Criteria is: Assuming that in Rheumatology, an expert Rheumatologist will be able to diagnose the disease based on an accurate history, in about 60% of cases, and if this definite history could be followed thorough physical examination, this probability will increase to 90%. And we know that a diagnosis of GPA can be made by applying the above criteria, when it is not possible based on the history and clinical examination, it made another diagnosis. Therefore, in none of the above studies, I did not make a special effort to determine the degree of specificity of the Criteria, despite the "Entry Criterion" (no other diagnosis upon history and physical examination can better explain the problems) will have a minimum specificity of 90%.

Clinical features

The Clinical Triad of the disease include involvement of the ENT (Ear, Nose, and Throat) organs, Lungs, and Kidneys [9]. The initial presentations of GPA most often (84-100%) indicate ENT involvement, possibly lungs involvement, and occasionally kidneys involvement [10]. Nasal problems include: nasal crusting, rhinitis, nasal obstruction, runny nose, smell disturbances, purulent/bloody nasal discharge, epistaxis, nasal ulcer, severe nasal pain, nasal septal perforation and saddle-nose deformity. Sinusitis is not only the most common finding at initial presentation of GPA (#70%) but also in the clinical feature of the disease chronic rhino-sinusitis is the classic ENT finding in this disorder [11]. We need to know that the sinusitis that manifests itself in GPA is basically an atypical (AtS) sinusitis. I, the corresponding author of this article, after much study, was able to collect and classify ten cases of unusual/atypical sinusitis, which are: Recurrent sinusitis, Chronic/intractable sinusitis, Sinusitis along with sinus mass, Sinusitis along with rhinitis, Sinusitis along with otitis, Sinusitis along with orbital cellulitis, Sinusitis along with dacryo-cystitis, Sinusitis along with mastoiditis, Sinusitis with severe pain in the nose, and pan-sinusitis. Each of the above AtS manifests itself in a patient, and after the initial examination and evaluation of that patient, we cannot find any suitable/justifiable disease as the cause of that sinusitis, we have to evaluate him/her for GPA [6]. It is important to know that recurrent sinusitis refers to sinusitis that recurs more than three times during a season, as well as chronic or refractory sinusitis that does not respond to treatment with a compatible broad-spectrum antibiotic for more than three weeks [12]. I did not find a specific definition for pan-sinusitis, so I decided to definite it myself as pan-sinusitis is a sinusitis that involves at least three separate sinus

cavities or at least two types of sinuses around the nose. AtS can be occurred due to opportunistic bacterial infections and/or fungal infections especially Mucormycosis but secondary to an underlying disease/state such as diabetic ketoacidosis, advanced complicated diabetes mellitus, malignancies, hereditary and/or acquired immunodeficiency states (AIDS), organ transplantation especially bone marrow transplantation, chronic high dose corticosteroid therapy, chemotherapy/cytotoxic therapy and so on. It needs to be mentioned that one out of four cases with AtS can be the patient with GPA [6]. Ear involvements include: otitis media, mastoiditis, and vertigo. Otitis media is more common in serous otitis media than purulent otitis media, and the resulting hearing loss is more conductional than sensori-neural [13]. We need to know that the otitis media that manifests itself in GPA is basically an atypical otitis media with the abbreviation AtOM. I, the corresponding author of this article, after much study, was able to collect and classify six cases of AtOM, which are: Persistent/Refractory otitis media, Recurrent otitis media, Bilateral otitis media, Otitis media with sensory-neural hearing loss, Otitis media along with rhinitis and, Otitis media with mastoiditis. It needs to be mentioned that; Persistent or Refractory otitis media refers to otitis media that persists despite a month of treatment with broad-spectrum and appropriate antibiotics or recurs within one month of the above treatment. Also, Recurrent otitis media refers to otitis media that recurs at least three times in six months or at least four times in a year [14]. We have to know that recurrent bilateral serous otitis media is the classic ear involvement in this disease [15]. Each of the above AtOM manifests itself in a patient, and after the initial examination and evaluation of that patient, we cannot find any suitable/justifiable disease as the cause of that otitis media, we have to evaluate him/her for GPA. It should be noted that AtOM occurs following the same underlying diseases described for AtS above. "Oral necrotic ulcer" as the classic feature and "strawberry gum hyperplasia" as the pathognomonic picture of GPA can be seen in the mouth [16]. Ophthalmic involvements of GPA are divided into two main groups, which include Eyeball involvements and Orbital involvements. Eyeball involvements include: conjunctivitis, epi/scleritis, keratitis, corneal ulcer, uveitis, and retinal vasculitis. Orbital involvements include: proptosis, dacryocystitis, excessive tearing and ophthalmoplegia [17-19]. Usually GPA ocular feature can be a combination of two or more of above items. When we see all above ophthalmic problems in a case of GPA, it is called "Red eye syndrome" or "blood shot eye". Hoarseness and stridor due to upper airway obstruction especially subglottic stenosis are the most important clinical manifestations of laryngo-tracheal tract. Sometimes, subglottic stenosis is the only initial presentation of GPA [20,21]. Pulmonary involvement varies from asymptomatic to hemoptysis and even acute and severe alveolar hemorrhage with respiratory failure. In the Chest X-Ray and/or High-Resolution CT scan (HRCT) of lungs; nodules, cavities and fixed infiltrations are the most important findings [22,23]. If pneumonia has one of the following conditions; GPA can be mentioned as one of the most important underlying diseases as a cause of pneumonia, provided that other causes are rejected simultaneously: intractable pneumonia, recurrent pneumonia, multiple lobe pneumonia, pneumonia with cavitation, fleeting pneumonia, hemorrhagic pneumonia, and pneumonia along with sinusitis.

Renal involvement can vary from asymptomatic to vigorous azotemia/uremia due to rapidly progressive glomerulonephritis. In most cases with GPA; glomerulonephritis is not associated with immune complex depositions which is pathologically referred to focal/diffuse segmental/crescentic necrotizing pauci-immune glomerulonephritis, but, sometimes, interstitial nephritis and/or vasculitis and/or granulomatous inflammation are the only pathologic findings in kidney [24,25]. Kidney involvements include microscopic hematuria and/or RBC casts and/or proteinuria and/or Azotemia

Nowadays the GPA can be divided into two types include Limited GPA: (ENT± Lung) involvement and Systemic GPA: [(ENT± Lung) + Kidney] involvement.

With ENT and/or lung involvement; GPA is of limited type. Whereas, with ENT and/or lung involvement along with kidney involvement; we have GPA of systemic type. There is not any gender tendency in systemic GPA but limited GPA can be seen in women more than men.

Musculoskeletal manifestations of GPA include arthralgia/arthritis, and myalgia/myopathy [26]. Arthritis occurs in less than one-third of GPA patients. If it presents as symmetrical polyarthritis of small and large joints in both upper and lower limbs with positive RF, it is similar to Rheumatoid Arthritis. Arthritis in the form of asymmetric oligo-arthritis of large joints of the lower limbs indicates similarity to Reiter's Syndrome, and acute migratory polyarthritis shows a picture that mimics Acute Rheumatic Fever.

GPA Skin involvement is pathologically a leukocytoclastic vasculitis whose clinical picture includes: palpable purpura, ulcer, nodule, papule, vesicle, urticaria, livedoreticularis, erythema nodosum, pyoderma gangrenosum, and hemorrhagic blisters. Most of these skin features occur in many vasculitis, but hemorrhagic blisters are rarely seen in another vasculitis [27].

Neurologic manifestations of GPA include: polyneuropathy, mononeuritis multiplex, cranial neuropathies (cranial nerves 2, 6, 7), cerebro-vascular accident (CVA), headache due to meningeal inflammation, and rarely CNS mass and even diabetes insipidus [28].

Gastro-intestinal (GI) involvement of GPA can be asymptomatic but enterocolitis with the presentations of abdominal pain and diarrhea, GI bleeding, ulcer, perforation, cholecystitis, ascites, pancreatitis, pancreatic mass and perianal ulcer are all the other GI features [29].

Just the opposite of other vasculitis diseases, in GPA non-coronary heart disease is more common than coronary heart disease and pericarditis is the most common cardiac manifestation of GPA. Other cardiac manifestations are: myocarditis with pictures of heart failure and/or arrhythmias, endocarditis, valvulitis with different clinical valvular disease, coronary vasculitis with manifestations of angina pectoris and/or myocardial infarction, arrhythmias and conduction defects.

Ureteral obstruction, hemorrhagic cystitis, granulomatous prostatitis, urethritis, epididymitis/orchitis and penile necrosis are all genitourinary manifestations of GPA [30].

It is believed that proptosis in conjunction with ENT or lung disease or glomerulonephritis is highly suggestive of the GPA [11], [31].

It also needs to be mentioned that almost all cases with vasculitis including proptosis or sino-nasal destruction or saddle-nose deformity

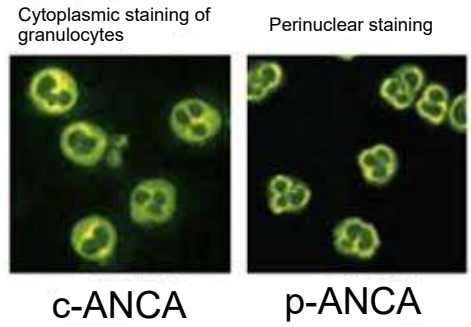

Figure 1: ANCA patterns; c-ANCA versus p-ANCA.

or subglottic stenosis are the cases of GPA. The combination of saddle-nose and subglottic stenosis along with rhinitis and/or nasal ulcer and/or bloody nasal discharge with crusted nose in a patient is compatible with diagnosis of GPA, whereas the pure combination of saddle-nose and subglottic stenosis without nasal mucosal ulcer, rhinitis or sinusitis is compatible to Relapsing Poly-Chondritis (RPC). Tuberculosis, Leprosy, carcinoma, lymphomatoid granulomatosis, lymphoma, congenital syphilis, cocaine abuse and nasal trauma and surgery are the other causes of saddle-nose deformity [32].

Para-clinical features

Cell Blood Count (CBC), Urine Analysis (U/A), Blood Urea Nitrogen (BUN), Creatinine (Cr), ESR/CRP, Liver Function Test (LFT), ANCA serology, sinuses and lungs imaging and pathology are all para-clinical evaluations that have to be done in a case suspected to be involved in GPA.

ANCA can be checked by Immunofluorescence (IF) assay with more sensitivity and ELISA with more specificity. When a patient with GPA is evaluated for ANCA by IF assay If he/she is positive for ANCA, while this method confirming the existence of ANCA, also identifies and expresses its various patterns, which are: C-ANCA: cytoplasmic-ANCA, P-ANCA: perinuclear-ANCA (Figure 1) and (non-c, non-p) ANCA: atypical-ANCA. The ELISA method, while identifying ANCA, is able to differentiate the types of ANCA depending on its substrate, which PR3-ANCA: anti-Proteinase 3-ANCA, MPO-ANCA: anti-Myeloproxidase-ANCA, and Others are exactly the same types. C-ANCA substrate is usually PR3, so it is also called anti-PR3, and P-ANCA substrate is basically MPO, so it is also called anti-MPO. ANCA is positive in 90% of the cases with active systemic GPA whereas, it is positive in about 60% of the cases with limited GPA. We have to know that about 90% of ANCAs in GPA are C-ANCA and C-ANCAs in GPA are anti-PR3 in about 90% of the cases. Knowing the predictive value of a positive C-ANCA is very important for the possible occurrence of GPA in the future, such as: the probability of developing a systemic disease with a positive C-ANCA towards GPA is less than 30%, and in chronic sinusitis less than 15%, whereas in acute glomerulonephritis this probability is more than 90% and may even be 98%.

Here we should mention a group of vasculitis diseases called ANCA-Associated Vasculitidies (AAV), including: Granulomatosis with Polyangiitis (GPA), Microscopic Polyangiitis (MPA), Eosinophilic Granulomatosis with Polyangiitis (EGPA) or Churg-Strauss Syndrome (CSS), and finally Renal Limited Vasculitis (RLV). These have three characteristics in common, which are: Positive ANCA, Small Vessel Vasculitis (SVV), and Focal necrotizing pauci-immune Glomerulonephritis. It needs to be mentioned that ANCA in other members of AAV e.g. MPA, EGPA and RLV most often is P-ANCA and it is usually anti-MPO. It is worth mentioning here that ANCA positivity is not only seen in AAV but also it can be seen in many other diseases and drugs therapy [33,34].

The main pathological findings in the GPA, namely small vessel vasculitis, granulomatous inflammation, and necrosis, refer to the GPA Pathologic Triad. We have to know that granulomatous inflammation can be seen in EGPA too but prolonged history of asthma and blood/tissue eosinophilia in EGPA can distinguish it from GPA, and also the absence of granulomatous inflammation in the pathology of MPA and low incidence of ENT involvement (<30%) in this disease may differentiate it from GPA. Knowing that proptosis, saddle-nose deformity, sino-nasal destruction, and subglottic stenosis can all be found in GPA, but their reporting is rare in other members of the AAV group, also helps to differentiate GPA from other AAV diseases.

The proper areas for biopsy in patients with suspected GPA include: ENT (especially sinuses), skin, kidneys, and lungs. Within ENT we can make a biopsy from nose, ear, sinuses, orbital fossa and so on. We need to know that the best site for a biopsy in the ENT organs is the involved paranasal sinus, which of course is not possible without sinus endoscopy. However, in the opinion of ENT Specialists, the nasal biopsy is a more suitable option because it is available and biopsy is easy to perform and does not require endoscopy under general anesthesia. It should be borne in mind that the nasal sample is small, non-specific or negative for pathologic evaluation of GPA but it is good for ruling out the malignancies and infections involving nose. Skin sample can show leukocytoclastic vasculitis and renal biopsy usually shows focal segmental pauci-immune glomerulonephritis. We should know that in GPA patients with pulmonary involvement, the lung biopsy has the highest percentage of definitive pathological findings to confirm the diagnosis of GPA compared to the other biopsies mentioned above, with positivity of open lung biopsies more than 90, and of course trans-bronchial biopsy less than 10%, whereas the ENT biopsy positivity is about 50% but it is accessible and less invasive [35]. Nowadays, because open lung biopsy requires open thoracic surgery, this biopsy is rarely performed in GPA patients. However, in rare cases, despite examining all the other options and

applying all the Diagnostic Criteria, while the GPA diagnosis is not confirmed, one or more differential diagnoses are still considered, open lung biopsy is the only option.

Results and Diagnosis

Upon the clinical/laboratory/imaging judgement of an expert Rheumatologist in cooperation with an expert otolaryngologist and an expert infectious disease specialist the diagnosis of GPA can be established.

Most Rheumatologists can only diagnose the advanced cases of systemic GPA involving the ENT, lungs and kidneys with vasculitic features including palpable purpura, hemorrhagic blister, necrotic ulcers and mono-neuritis multiplex along with ANCA positivity and the presence of SVV and granulomatous inflammation in pathology. Whereas, the cases of limited GPA in early stages without vasculitic features along with ANCA negativity and the absence of SVV and granulomatous inflammation in pathology can only be diagnosed by expert Rheumatologists.

Be aware that there have been several Criteria for Classifying/Diagnosing Wegener's Granulomatosis (before 2011) or Granulomatosis with Polyangiitis (from 2011 onwards). Some of the proposed Criteria are not specific to GPA and are in fact used to Classify ANCA Associated Vasculitis (AAV). These Criteria Classify and Differentiate GPA, MPA, and EGPA in parallel or sequentially, so they are not discussed. We refer here only to those Criteria that are specific to GPA.

Well-known Criteria have been presented for Classifying/Diagnosing Wegener's Granulomatosis or GPA that are:

- The 1990 American College of Rheumatology (ACR) Classification Criteria for Wegener's Granulomatosis [36].
- The 2007 European Medicine Agency Algorithm (EMA) Diagnostic Criteria for systemic GPA [37].
- The ACR/European League Against Rheumatism (EULAR) Provisional 2017 Classification Criteria for GPA [38].

Whereas, unknown and unfamiliar Criteria have been presented for Diagnosing GPA, few physicians are aware of their existence, which are:

- The Iran Criteria for Early Diagnosis of GPA [39].
- The 2017 ACR/EMA Revised Criteria for Too Early Diagnosis of GPA [40].

Discussion

The 1990 ACR Classification Criteria for Wegener's Granulomatosis (Table 1) is the oldest Criteria in this field, that is:

With at least two of the above four criterions, the patient is classified as a case of Wegener's granulomatosis [36]. As you can see, this Criteria is for the Classification of Wegener's Granulomatosis, not for its Diagnosis, and includes a clinical criterion, an imaging criterion, a laboratory criterion, and a pathological criterion with the same value. This Criteria ignores many important and key clinical findings. It does not mention ANCA, and by applying this Criteria; in imaging the values of nodules, cavities, or pulmonary infiltrations are the same. The only laboratory criterion is the presence of hematuria with or without RBC cast in the urine, and in pathology only granulomatous inflammation is mentioned, whereas SVV and necrosis have been ignored. It should be noted that granulomatous inflammation cannot be seen in the pathology of more than 40% of patients with Wegener's granulomatosis, whereas this pathological item cannot be seen in almost all cases with Microscopic Polyangiitis (MPA) [39]. Here it is necessary to explain that in cases where the pathology lacks granuloma, if there are two of the first three criterions of above Criteria, both Wegener's Granulomatosis and MPA can be classified by this Criteria, in which case the Criteria will not be able to distinguish between the two diseases, so its specificity is too much low, less than 60%. It should be noted that the sensitivity of the 1990 ACR Classification Criteria for Wegener's Granulomatosis is not sufficient (<80%) too [39]. Therefore, more than 20% of the patients with Wegener's Granulomatosis will never be classified by this Criteria, and sometimes by applying this Criteria the lag period between the initial presentation of Wegener's Granulomatosis and classification of it may be a few years. Therefore, the above Criteria should be excluded without any support.

The second Criteria discussed here is the 2007 EMA Criteria (Table 2), which has been made only for diagnosis of Systemic GPA in the absence of Biopsy, that is:

• Oral ulcer or bloody/purulent nasal discharge
• Nodule, fixed infiltration or cavity in chest X-Ray
• ≥ 5 RBC with or without RBC cast in urine analysis
• Granuloma in pathology

Table 1: The 1990 ACR classification criteria for Wegener's granulomatosis.

• Lower airways (chest X-Ray) findings
• Upper airways (ENT) findings
• Glomerulonephritis and
• Positive ANCA

Table 2: The 2007 EMA criteria for diagnosis of systemic GPA, where pathology is not available.

You should know that the initial presentation of GPA most often contains ENT findings, may be pulmonary involvement, and occasionally begins with kidney problems [39,40]. Therefore, it takes months or even years to see simultaneous involvement of all above three organs. We also note that all the above criterions will be required to establish a systemic GPA diagnosis by this Criteria, so its sensitivity to diagnose the disease will be very low, especially for months or even years after the initial presentation of GPA. In addition, it is clear that in the absence of pathological findings, the specificity of the Criteria will decrease sharply too [37]. Thus, this Criteria is completely defenseless and has to leave the ring of the Criteria competition.

The ACR/EULAR Provisional 2017 Classification Criteria (Table 3) can classify a patient as a case of GPA when at first the presence of small vessel vasculitis is confirmed in the pathological examination of the individual and then the minimum score (≥ 5 scores) required for the Criteria is obtained. This Criteria includes two groups of clinical and para-clinical criterion, which are:

Achieving at least 5 points from the above scoring system by a patient with small vessel vasculitis classifies him/her as a case of GPA [38].

Observable problems and defects in this Criteria according to the author of the article (ISA) are:

a. Necessity of pathological examination in all patients to prove the presence of small vessel vasculitis at the beginning step.

b. This Criteria ignores the kidneys and does not provide any criterion in this regard.

c. Assign the highest positive score to C-ANCA or anti-PR3 ANCA positivity

d. Assign the highest negative score to nasal polyps

e. Assign +3 points to Granuloma on Biopsy

f. Assign +1 point to Red or Painful eyes

a. Obviously, the best strategies and Criteria in medicine are those that start with the simple, low-cost, and non-invasive steps. In other words, complex, costly, and aggressive actions are usually related to the final stages of these strategies and Criteria.

b. One of the most important organs affected by GPA is the kidney, but this Criteria does not provide any renal criterion, so its credibility is reduced. In addition, without such a criterion, it will no longer be able to identify and distinguish systemic GPA from limited.

c. Early manifestations of GPA often begin with ENT involvement, but pulmonary involvement may initiate the disease and, although occasionally, the disease begins with renal involvement. We know that ANCA is positive in limited GPA (without renal involvement) up to 60% of cases and in active systemic GPA up to 90%. Also, we know that ANCA in GPA is of C-ANCA or anti-PR3 type in 80–90 % of cases [39,40]. Everyone knows that ANCA is not specific to GPA and is found in both MPA and EGPA too. It can also be less positive in many different diseases and medications. We also know that ANCA is predominantly a P-ANCA in cases other than GPA. Knowing the predictive value of a positive C-ANCA is very important for the possible occurrence of GPA in the future, such as: the probability of developing a systemic disease with a positive C-ANCA towards GPA is less than 30%, and in chronic sinusitis less than 15%, whereas in acute glomerulonephritis this probability is more than 90% and may even be 98% [39,40]. With this background information and knowing that in the early stages of GPA (months and even years), the involvement is mainly related to ENT, especially sinusitis, and to a lesser extent pulmonary and much less renal, so the ANCA diagnostic value and its positive predictive power in the early stages of GPA is much less than the later and advanced stages of the disease. Therefore, assigning the highest value (5 points) to C-ANCA in this Criteria will greatly reduce its sensitivity especially in early stages. On the other hand, due to the non-specificity of C-ANCA for GPA, this high score to C-ANCA will greatly reduce the specificity of the above Criteria too [39,40].

d. As for nasal polyps, it should be noted that its prevalence in general population is about 2.7% and especially in the elderly 5%.

Clinical Criteria:
• Bloody nasal discharge, nasal ulcers, nasal crusting, or sino-nasal congestion with +3 points
• Nasal Polyps with – 4 points
• Hearing loss or reduction with +1 point
• Cartilaginous involvement with +2 points
• Red or Painful eyes with +1 point
Para-clinical criteria:
• Positive C-ANCA or anti-PR3 ANCA with + 5 points
• Eosinophil count >109/L with – 3 points
• Nodules, mass, or cavitation on chest imaging with + 2 points
• Granuloma on Biopsy with + 3 points

Table 3: The ACR/EULAR provisional 2017 classification criteria for GPA.

We know that GPA is mainly prevalent in middle-aged and elderly people and its prevalence is 3 per 100,000. Therefore, the prevalence of nasal polyps is more than 1600 times the prevalence of GPA and we can see nasal polyps simultaneously and accidentally in at least 5% of GPA patients. Therefore, assigning 4 negative points to nasal polyps alone reduces the sensitivity of the ACR/EULAR Criteria by 5% without adding a percentage to its specificity [41].

e. In the best-case scenario, ENT biopsy specimens help diagnose GPA in less than 50% of cases, and the highest reported granuloma rate in GPA pathology has been about 60%. Of course, this percentage is very high in lung biopsy specimens, but nowadays, due to the less need for diagnosis and also the invasiveness of lung biopsy, this operation is performed too much less. Therefore, it is very clear that assigning 3 points to the granuloma will greatly reduce the sensitivity of the Criteria [42].

f. I should also mention that since a significant percentage of people suffer from red or painful eyes on a daily basis due to stress, insomnia, a lot of reading, looking too much at the LED screen of a mobile phone or laptop, watching TV, and the presence of pollutants and particulate matter in urban air and viral infections, even assigning a point to red or painful eyes, is not a logical justification where proptosis or dacryo-cystitis could be assigned.

Finally, the above Criteria itself states that it is intended to classify the disease, not to diagnose it.

Therefore, just as the 1990 ACR Criteria and the 2007 EMA Criteria that were dropped, it is better to forget the ACR/EULAR Provisional 2017 Classification Criteria for GPA.

But here are two Criteria for "Early Diagnosis" and "Too Early Diagnosis" of GPA, which have been designed by the corresponding author of this article due to years of study and experience in visiting and following up these patients.

- The Iran Criteria for Early Diagnosis of GPA (Table 4)
- The 2017 ACR/EMA Revised Criteria for Too Early Diagnosis of GPA (Table 5)

In the presence of Entry Criterion (no other diagnosis upon history and physical examination can better explain the problems) with at least 4 points out of 11 the diagnosis of limited GPA will be established, whereas for definite diagnosis of systemic GPA we need at least 5 points out of 11 [39].

We know that with normal/negative pathology and/or negative ANCA, GPA cannot be ruled out. With normal ENT or lung or kidney, GPA cannot be ruled out either. Only when all of the organs of ENT, lung and kidney together are not involved, the diagnosis of GPA will be ignored.

The Granulomatous Diseases of nose and paranasal sinuses in differential diagnosis of GPA include [43]:

- Infections: Tuberculosis, Leprosy, Rhinoscleroma, Syphilis, Histoplasmosis, Leishmaniasis, Rhinosporidiosis, Mucormycosis,
- Vasculitidies: Churg-Strauss syndrome,
- Malignancies: Lethal midline granulomatosis, Non keratinizing nasopharyngeal carcinoma, and
- Others: Sarcoidosis, Cocaine abuse, and so on.

In overall the most important differential diagnoses of limited GPA involved in ENT are Mucormycosis, Angiocentric lymphoma and Cocaine abuse whereas the most important differential diagnoses of systemic GPA are Mucormycosis, Churg-Strauss syndrome, Microscopic Polyangiitis, Sarcoidosis and Tuberculosis.

You have to know that the hyphae of Mucorales is air-born and exists everywhere around us. So, the detection of it within mucosal discharge is not diagnostic. Only the histologic detection of hyphae and positive culture of it can be diagnostic and confirmation of the diagnosis of Mucormycosis needs two steps: Step I: Histologic detection of hyphae and Step II: Culturable potential of hyphae. Almost all patients with Mucormycosis have an underlying disease as predisposing factor include [44]:

Advanced uncontrolled diabetes mellitus, Ketoacidosis, Malignancies especially Leukemia/Lymphoma and Myeloproliferative disorders, Hereditary and/or Acquired Immuno-Deficiency States (AIDS), Chronic high dose corticosteroid therapy, Chemotherapy and Cytotoxic therapy, Organ transplantation (especially bone marrow), Deferoxamine therapy, Iron overload/ Hemochromatosis, IV drug abuse, Malnutrition, Burns and so on. We know that one-fifth to one-third of the different population have Diabetes Mellitus and it is the most common underlying disease for Mucormycosis [39]. The Diabetes Mellitus can be predisposing factor for Mucormycosis when it is advanced uncontrolled especially when results in ketoacidosis. So, a small percentage of the patients with Diabetes Mellitus involves in Mucormycosis. I think there is over-diagnosis of Mucormycosis and under-diagnosis of GPA in the world. Many cases of GPA that have been diagnosed by me had previous wrong diagnosis of Mucormycosis [45]. From now on, both in the COVID-19 pandemic and later, COVID-19 should be considered as an important differential diagnosis of GPA because it can be a systemic disease involving the ENT, lungs, kidneys, heart, brain, skin, etc. Existence of necrotic ulcers in the mouth or nose, perforation of the nasal septum, saddle-nose deformity, destruction of the paranasal sinus walls, presence of a mass in the sinuses, proptosis of the eyes, presence of cavity in the lungs, and positive ANCA test and finally granuloma in pathology; each alone can benefit from a GPA diagnosis, while having more than one of the above will be entirely in the GPA's favor [46].

• ENT Criteria up to 3 points
• Lung Criteria up to 2 points
• Kidney Criteria up to 1 point
• ANCA Criteria up to 2 points
• Pathological Criteria up to 3 points

Table 4: The Iran criteria for early diagnosis of GPA.

By application of The Iran Criteria for Early Diagnosis of GPA only about 50% of our cases with GPA became systemic, due to the earlier diagnosis and management of GPA. Whereas in the world, about 80% of cases with GPA are systemic with kidney involvement [39]. Despite this achievement the lag period between initial presentation of GPA and the confirmation of diagnosis has been more than one month yet.

You have to know that with a little change within Iran Criteria a new Criteria is created by the author of this letter called the 2017 ACR/EMA Revised Criteria for Too Early Diagnosis of GPA (Table 5) by which the diagnosis of GPA can be established earlier within the first month of initial presentation of the disease [40]. For making an accurate cost-effective diagnosis the author (ISA) proposes a four-step practical Guideline approaching towards the diagnosis of GPA too. The physician must go through the steps one by one and if the 2017 ACR/EMA Revised Criteria for Too Early Diagnosis of GPA is not yet satisfied in each step, go through the next [40].

Finally, the corresponding author of this letter as the creator of The Iran Criteria for Early Diagnosis of GPA would like to ask ACR, EMA, EULAR, APLAR and all of the Rheumatologists in the world to evaluate the 2017 ACR/EMA Revised Criteria for Too Early Diagnosis of GPA.

Guideline

Practical Guideline approaching towards the diagnosis of GP

Step I:

- History and physical examination by Rheumatologist and otolaryngologist
- CBC, Blood urea nitrogen/Creatinine, ESR, Urinary Analysis, ANCA serology, Liver Function Tests, RT-PCR test
- Sinuses X-Ray, Chest X-Ray

Step II:

- CT-scan of sinuses (spiral PNS CT)
- Spiral HRCT of lungs

Step III:

- ENT endoscopy especially of sinuses
- ENT biopsy especially of sinuses and/or nose

Step IV:

- Other sites biopsy
- Skin
- Kidney
- Lung: especially thoracoscopy or open thoracotomy

Conclusion

The 1990 ACR Classification Criteria for Wegener's Granulomatosis

- It is to classify the disease, not to diagnose it
- It does not have enough sensitivity and specificity
- Due to the long lag periods between initial presentation of the disease and the time of diagnosis, it is not a good Criteria for early detection of Wegener's Granulomatosis.

Therefore, this Criteria is categorically rejected by the author.

The 2007 EMA Diagnostic Criteria for GPA:

- It is only for diagnosis of systemic GPA, not limited GPA
- It can be used in the absence of biopsy, and
- It needs all four criterions for diagnosis of Systemic GPA, so its sensitivity and specificity are terribly low and it can detect the disease in advanced stages.

Therefore, this Criteria is also strongly discarded by the author.

The ACR/EULAR Provisional 2017 Classification Criteria for GPA:

• ENT Criteria[c] up to 4 points
• Lung Criteria[d] up to 2 points
• Kidney Criteria[e] up to 1 point
• ANCA Criteria[f] up to 2 points
• Pathological Criteria[g] up to 2 points
[a]Entry Criteria: no other prominent diagnosis such as tuberculosis, EGPA (CSS), MPA, Mucormycosis, Cocaine abuse, and RPC can explain the condition according to the patient's history and physical examination [40]; [b]The definite diagnosis of Limited GPA (ENT and/or Lung involvement) can be established if the patient fulfills ≥ 4 points out of 11, whereas with at least 5 points out of 11 the diagnosis of Systemic GPA [(ENT and/or Lung) along with Kidney involvement] will be defined. [c]ENT points: more than one episode of bloody nasal discharge with nasal crusting or nasal ulcer or severe nasal pain: 1 point, oral necrotic ulcer: 1 point or strawberry gum hyperplasia: 2 points totally up to 2 points for oral cavity, persistent/intractable or recurrent sinusitis: 1 point, persistent/intractable or recurrent or bilateral otitis media or otitis media with sensory-neural hearing loss: 1 point, proptosis: 2 points, saddle-nose deformity: 2 points, subglottic stenosis: 2 points, in PNS CT scan: pan-sinusitis or sinus mass: 1 point, sino-nasal destruction: 2 points, mastoiditis: 1 point. Attention please: if sinusitis is repeated in both history/physical examination and PNS CT scan just PNS CT scan score is acceptable; [d]Lung points: hemoptysis: 1 point, In CXR or HRCT: nodule: 2 points. cavity: 2 points. fixed infiltration: 1 point; [e]Kidney points: hematuria (≥ 5 RBC or > +1 blood) or proteinuria (>+1) or RBC cast: 1 point; [f]ANCA points: positive ANCA or P-ANCA or anti MPO-ANCA: 1 point. positive C-ANCA or anti-PR3-ANCA: 2 points; [g]Biopsy points: small vessel vasculitis without eosinophilia: 1 point. granulomatous inflammation without eosinophilia: 2 points.

Table 5: The 2017 ACR/EMA revised criteria for too early diagnosis of GPA[ab].

- It is to classify the disease, not to diagnose it
- It does not have enough sensitivity and specificity in early stages of GPA
- This Criteria ignores the kidneys and does not provide any criterion in this regard, and
- According to the author of article (ISA), this Criteria has several other drawbacks that were mentioned in the discussion.

Therefore, this Criteria, like the above two Criteria, is seriously refused by the author.

"The Iran Criteria for Early Diagnosis of GPA", and "The 2017 ACR/EMA Revised Criteria for Too Early Diagnosis of GPA", both exactly with 100% sensitivity and high probably with more than 90% specificity are created, presented, and highly recommended by the author of the article, and are left to the judgment of the world's great Rheumatologists, especially researchers in the field of GPA. Finally, the golden sentence of this article is that if you want to diagnose GPA early or too early with high accuracy, it is recommended to apply these two Criteria.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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