

OPINION and IDEA

Rheumatoid arthritis no longer could be a major cause of multiple pulmonary nodules in post-ANCA era

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Rheumatoid arthritis (RA) is a multi-system disease characterized by chronic non-specific synovitis associated with rheumatoid factor (RF) or anti-cyclic citrullinated peptide (anti-CCP) positivity in most proportion of cases. Major target organs in RA are however diarthrodial joints with resultant destruction and ankylosis. RA has pleuroparenchymal involvement with varied manifestations, which includes organizing pneumonia, interstitial fibrosis, airway disorders such as bronchiectasis and bronchiolitis and pulmonary vasculitis and also rheumatoid nodules. (1)

On the other hand, Wegener's granulomatosis or recently renamed as Granulomatosis with polyangiitis (GPA) is potentially life threatening condition with estimated incidence of 8.5 in a million in general population (Norfolk, primer p.417). Peter McBride (1854–1946) first described the condition in 1897, Heinz Karl Ernst Klinger (1907) added information on it, but the classic picture was presented by Friedrich Wegener (1907–1990).

It is a necrotizing granulomatous vasculitis belonging to a major category of ANCA-associated vasculitides which involves sinuses and lung in classic forms. Pulmonary manifestations of Wegener's granulomatosis could be as lung nodules, which can be cavitate in most instances, acinar shadows which may represent alveolar hemorrhage, mediastinal lymphadenopathy and pleural effusion (1).

Detecting antibodies most specific for these conditions revolutionized the issue of diagnosis and had a good impact on determining prognosis. Impact of ANCA (antineutrophil cytoplasmic antibodies) on whole body of vasculitides was so great so that in a general category suggested by some authors, vasculitides are divided into two major categories of ANCA associated and non-ANCA associated vasculitis. It is believed that ANCA may have

pathogenic role in pathophysiology of ANCA associated vasculitis.

Anti-neutrophil cytoplasmic antibodies (ANCAs) are a group of autoantibodies, against antigens in the cytoplasm of neutrophil granulocytes and monocytes. They are seen in a number of autoimmune disorders, but are highly associated with ANCA-associated vasculitides. ANCAs were basically described by Davies et al. in 1982 in some kind of necrotizing glomerulonephritis.

Clinical manifestation of GPA is also similar to RA in a plenty of cases presenting with symmetric polyarthritis. GPA and RA are among the major differential diagnosis in case of multiple pulmonary nodules (MPN).

Diagnosis of both RA and GPA is clinical in most instances based on pattern of clinical manifestation, pathological investigation and other laboratory investigations may confirm the diagnosis.

Classification criteria of GPA which proposed in 1990 is based mainly on clinical aspects of Painful or painless oral ulcers or purulent or bloody nasal discharge, Abnormal chest radiograph such as nodules, fixed infiltrates, or cavities, Microscopic hematuria or red cell casts, and of course granulomatous inflammation on biopsy specimen. Based on the anatomic ELK classification (2) (E for ear, nose and throat, L for lung and K for kidney) of Wegener's granulomatosis, some patients have the L type with lung involvement only with sparing of the kidney and the upper respiratory tract.

A patient is said to be classified as Wegener's granulomatosis if at least two of these four criteria are present. The presence of any two or more criteria yields a sensitivity of 88.2% and a specificity of 92.0%.

On the other hand new classification criteria for RA are mainly based on clinical aspects. (ACR/ EULAR 2010).

In practice, patients frequently are diagnosed with RA with clinical picture of symmetric chronic polyarthritis with RF positivity in whom later features of a vasculitis ensues. Although RA per se

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can manifest as a necrotizing vasculitis but this feature is late in the course of disease and usually evolve in the context of full-picture RA.

Most clinicians are familiar with classic differential diagnosis of MPN notably lymphoma, bronchiolitis obliterans organizing pneumonia, RA, GPA, sarcoidosis, fungal infiltrates and lung metastasis.

Although tissue diagnosis is cornerstone for diagnosis, ANCA has a pivotal role in differentiating GPA from other diagnosis. The combination of C-ANCA and PR3-ANCA has a high positive predictive value for ANCA-associated vasculitis, particularly Wegener's granulomatosis. Practically decisions are made individually by collecting clinical and laboratory investigations and biopsy of nodules are preserved for occasional patients.

Renal involvement as glomerular hematuria is a discriminative index differentiating clinically GPA from RA. But it is evident in only 60-70% of patients with GPA at presentation. In limited GPA by definition clinical involvement of kidneys are absent. But limited GPA in lung, eye, and kidney has been reported.

Based our long term clinical observations, we believe that in pre-ANCA era, it is likely that many cases of GPA were misdiagnosed as RA due to lack of access to ANCA and new modern techniques of investigations. So a global attention and reconsideration is justified regarding classic data on MPN and RA. In our routine practice if a patient with clinical feature of RA show MPN in his or her chest radiograph the likelihood that he or she have had GPA is considered to be very high especially when the patient shows c-ANCA activity. (3)

We believe that in similar clinical setting, based on former radiographic and clinical data when modern rheumatology have not been developed the most pertinent diagnoses were RA. Also based on our longitudinal observations, we think the incidence of MPN in RA is very low, considering relative higher frequency of RA in respect to GPA, we have hardly seen any case of MPN secondary to RA during more than 10 years of practice. On the other hand, we had frequent cases of MPN with final diagnosis of GPA.

We recall that there are reports of Wegener's granulomatosis that develop in an established case of rheumatoid arthritis although this association is very rare.

In the reported cases the majorities were women and RA preceded GPA in all cases except one. (1, 4-7) In most of them there is not enough information of initial evaluation of cases about vasculitis especially GPA and may be some of them were the first GPA.

We think when a patient who suspected to have RA presented by MPN we have to evaluate him for vasculitis at least by ANCA, so that positive c-ANCA is actually discriminative for GPA but this important tool was absent in pre-ANCA era. So most cases may be labeled enormously as nodular RA involving lungs(1). Poorer prognosis of so-called pulmonary nodular RA may be attributable to this missing fact.

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