Vital corner of diagnostic challenge: eosinophilic granulomatosis with polyangiitis or COVID-19 pneumonia?

The COVID-19 pandemic raises many alarms in the rheumatological era. Gianfrancesco et al reported the answer of an important question: the characteristics associated with hospitalization for COVID-19 in people with rheumatic disease. The data suggested that patients with rheumatic disease on prednisone dose of ≥10 mg/day were associated with higher odds of hospitalization, and vasculitis was the fourth common rheumatic disease among all of these patients.

Another essential concept is to be careful in the differential diagnosis of the patients presenting with symptoms and signs of COVID-19. Physicians should keep in mind the other infectious and inflammatory diseases during diagnostic procedures of these critical patients. Inevitably, COVID-19 ranks first in differential diagnosis of all patients with respiratory symptoms and signs in current pandemic days. The standard of reference for confirming COVID-19 relies on microbiological tests, such as real-time reverse transcription polymerase chain reaction (RT-PCR). A systematic review of the accuracy of COVID-19 tests reported false-negative rates up to 29% (equating to a sensitivity of 71–98%), based on negative RT-PCR tests which could turn out positive on repeated testing. Chest CT can be used as an auxiliary to RT-PCR for diagnosing COVID-19 pneumonia in the current pandemic context. The main CT feature of COVID-19 pneumonia is the bilateral patchy ground-glass opacities (GGOs) with peripheral predominance. On the other hand, GGO has many causes and one of these is eosinophilic granulomatosis with polyangiitis (EGPA). Herein, we presented two patients who have been hospitalized with preliminary diagnosis of COVID-19 but diagnosed as EGPA in hospitalisation period for COVID-19.

CASE 1
A male patient in his 20s was admitted to the emergency department with complaints of shortness of breath, cough and sputum. In the medical history of the patient, he had asthma for 3 years but he did not receive any asthma treatment. His shortness of breath deteriorated in the last month. He had no contact with any suspected or confirmed COVID-19 patient. Physical examination showed normal body temperature but diffuse bilateral rhonchi, and pulse oximetry revealed an oxygen saturation of 90% on ambient air. The results of his laboratory tests were as follows: white blood cell count (14.1×10^9/L and eosinophil count (2.89×10^9/L); haemoglobin level was 17.4 g/L and C reactive protein (26 mg/L). D-dimer, ferritin, erythrocyte sedimentation rate (ESR) and procalcitonin levels were normal. Nasopharyngeal swab was obtained from the patient for CoVID-19 RT-PCR after the chest CT revealed bilateral ground-glass opacifications (figure 1A). Due to the pandemic, spirometry (an aerosolising procedure) was deferred/skipped. He was hospitalized due to oxygen supplementation requirement and chest CT findings compatible with COVID-19. Hydroxychloroquine and azithromycin were commenced. However, RT-PCR chest CT findings compatible with COVID-19. Hydroxychloroquine was used as an auxiliary to RT-PCR for diagnosing COVID-19 pneumonia.

CASE 2
A female patient in her 40s with a history of untreated asthma for 20 years presented to the emergency department with shortness of breath, cough and wheezing. She was afebrile. Physical examination revealed diffuse rhonchi and pulse oximetry showed an oxygen saturation of 86% on ambient air. The results of her laboratory tests were as follows: white blood cell count (13.2×10^9/L) and eosinophil count (1.27×10^9/L) and ferritin level (20 mg/day). No relapse has been observed yet at the first month control.

antineutrophil cytoplasmic antibody (p-ANCA)/myeloperoxidase (MPO) (1:100 titer) positive. Mucosal thickening and opacities were seen in ethmoid and maxillary sinuses on paranasal CT (figure 1B). EGPA was diagnosed depending on coexistence of asthma, eosinophilia in peripheral blood, MPO-ANCA positivity and paranasal CT abnormality (Table 1). We started treatment with 50 mg/day prednisolone and inhaled corticosteroid and long-acting beta agonist (LABA) combination. His asthma was under control, and shortness of breath and eosinophilia regressed under this treatment. Prednisolone dose tapered to 20 mg/day. No relapse has been observed yet at the first month control.

Figure 1 (A) Axial thorax CT image shows focal ground-glass opacities (B) Mucosal thickening and opacities are seen in ethmoid and maxillary sinuses. (C) Bilateral ground-glass opacifications that almost completely disappeared with corticosteroid on axial CT scans of the chest lung window (before and after treatment). (D) Lymph nodes that disappeared (red arrows) after treatment on axial CT scans of the chest mediastinal window (before and after treatment).
asthma, recurrent episodes of sinusitis and nasal polyp surgery in the patient's medical history, and eosinophilia in peripheral blood raised the question of whether the patient had EGPA. ANCA tests results were negative. Paranasal CT showed a right-maxillary sinus retention cyst. We diagnosed EGPA and put her on 50 mg/day prednisolone and inhaled corticosteroid-LABA combination treatment. Asthma symptoms and eosinophilia resolved under treatment. Similarly, prednisolone dose tapered to 20 mg/day. No relapse occurred (table 1).

In current pandemic days, COVID-19 positions the first in differential diagnosis of all patients with respiratory symptoms and signs. RT-PCR plays a vital role in the diagnosis of COVID-19. However, its lower sensitivity, insufficient stability and relatively longer processing time can cause delay in disease control. Chest CT is another main diagnostic tool for COVID-19 with overlapping of CT imaging findings between COVID-19 and other diseases, vascular dilatation, traction bronchiectasis, subpleural bands, air bronchogram, vascular sign and bronchus distortion may be seen in the progressive stage of the disease. Besides these findings, vascular dilatation, traction bronchiectasis, subpleural bands, air bronchogram, vascular sign and bronchus distortion are other common signs of COVID-19 pneumonia. On the other hand, pleural fluid, enlarged mediastinal lymph nodes, cavitation and tree in bud appearance are uncommon findings for COVID-19. Although presence or absence of these findings can help in the diagnosis of COVID-19 pneumonia, different manifestations of COVID-19 can cause diagnostic challenge.

Presence of both central and peripheral focal GGOs and enlarged mediastinal lymph nodes on the CT images of our cases was atypical for COVID-19 pneumonia. Nevertheless, RT-PCR tests results were negative twice with 24-hour intervals. Furthermore, eosinophilia in peripheral blood in both cases is an unexpected feature of COVID-19. EGPA is a disease characterised by systemic necrotising vasculitis and eosinophilia that can occur in patients with asthma. Asthma is the major EGPA characteristic affecting 91%–100% of patients, most often before systemic vasculitis starts. While p-ANCA positivity is about 40% in patients with EGPA, c-ANCA positivity is less than 10%. EGPA was the more appropriate diagnosis since our cases had asthma history, eosinophilia and migratory infiltration in the lung.

To the best of our knowledge, there is only one case in the English medical literature who was hospitalised with suspicion of COVID-19 and was diagnosed with EGPA. In that case, the patient had eosinophilia, bilateral GGO in lung and skin lesion, but he had no asthma and ANCA tests results were negative. In addition, the skin biopsy specimen revealed perivascular infiltrates with eosinophils.

In this pandemic situation, CT undoubtedly plays an important role in the early identification of COVID-19 pneumonia. Typical CT features include predominant peripheral GGOs with multifocal distribution. To investigate other causes of GGO in patients who have atypical CT findings for COVID-19 pneumonia with negative RT-PCR test result is important. In particular, asthma history and eosinophilia in peripheral blood prompt the need to be investigated for EGPA. Awareness of the similar clinical manifestations between EGPA and COVID-19 pneumonia is critical.

| 1990 ACR CCS classification criteria (4/6 for classification) | Case 1 | Case 2 | Draft ACR/EULAR Criteria for EGPA (>5 points for classification) | Case 1 (total score: 8) | Case 2 (total score: 11) |
|---------------------------------------------------------------|--------|--------|---------------------------------------------------------------|------------------------|------------------------|
| Asthma                                                        | Yes    | Yes    | Obstructive airways disease (+3)                             | +3                     | +3                     |
| Paranasal sinus abnormality                                   | Yes    | No     | Nasal polyps (+3)                                            | No                     | +3                     |
| Mononeuropathy (including multiplex) or polyneuropathy        | No     | No     | Mononeuritis multiplex or motor neuropathy (+1)              | No                     | No                     |
| Eosinophilia >10% on differential white blood cell count      | Yes    | Yes    | Eosinophil count >10³/mL (+5)                                | +5                     | +5                     |
| Biopsy containing a blood vessel with extravascular eosinophil | Not done | Not done | Extravascular eosinophil predominant inflammation/ increased eosinophils in bone marrow (2) | Not done | Not done |
| Non-fixed pulmonary infiltrates on roentgenography            | Yes    | Yes    | Microscopic haematuria (−1)                                  | No                     | No                     |
| c-ANCA or PR3-antibody positivity (−3)                         | Negative | Negative | c-ANCA or PR3-antibody positivity (−3)                         | Negative | Negative |

ACR, American College of Rheumatology; c-ANCA, cytoplasmic antineutrophil cytoplasmic antibody; CSS, Churg-Strauss syndrome; EGPA, eosinophilic granulomatosis with polyangiitis; EULAR, European League Against Rheumatism.
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