Laboratory findings support the diagnosis of MPO-Anca-associated vasculitis following SARS-CoV-2 vaccination

Maria Rosa De Cagna[1], Vincenza. Colucci[2], Norma Notaristefano[1], Maria Grazia Corallo[2], Katia Danza[1], Francesca Cianciotta[2], Luigi Francesco Pio Morrone[2], Marilina Tampoia[1]
[1]Clinical Pathology Unit, SS Annunziata Hospital, Taranto
[2]Nephrology Unit, SS Annunziata Hospital, Taranto

Questo contributo è stato in parte presentato al 54° Congresso nazionale SIBioC di Genova, 4-7 ottobre 2022, nella sessione Casi Clinici.

ABSTRACT

We report a *de novo* case of severe anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, following the mRNA vaccine for COVID-19, diagnosed on February 2022 in a Nephrology Unit of Southern Italy. The patient was a very young man (21-years-old) of Moroccan origin, who entered the hospital two times, a few days after the first and after the second administration of the BNT162b2 vaccine with fever, respiratory distress and papulo-erythematous/ purpuric lesions on limbs and trunk. The laboratory tests revealed: hypereosinophilia, increased creatinine, proteinuria, microhaematuria, increased levels of total IgE and a strong positivity to autoantibodies anti-myeloperoxidase (anti-MPO). Instrumental and biopsc examinations confirmed the diagnostic suspicion. An appropriate laboratory approach, together with clinical surveillance for vaccine immunological complications, should always be performed to help the diagnosis, the monitoring and the clarification of possible vaccine adverse effects.

Key words: *SARS-CoV-2 vaccines, ANCA-associated vasculitis, eosinophilic granulomatosis*

CASE REPORT

On January 2022, a 21-year-old man of Moroccan origin, with a reported history of bronchial asthma, entered the emergency room of "SS Annunziata" Hospital for respiratory distress and low-grade fever, occurred few days after the first administration of BNT162b2 mRNA vaccine against SARS-CoV-2. He was discharged with oral steroid and antibiotic therapy.

One day after the second dose of the same vaccine, on February 2022, he entered the hospital again due to worsening of respiratory symptoms, high grade fever, vomit, edema and papulo-erythematous/purpuric lesions on limbs and trunk (Figure 1). The initial laboratory tests revealed: hypereosinophilia (27.8%, 6.63x10^9/L; r.v. <7.0, <0.7 respectively), a systemic inflammatory process [C-reactive protein 130 mg/L (r.v. <5.0), fibrinogen 410 mg/dL (r.i. 200-400), D-Dimer 10.32 mg/L FEU (r.v. <0.5)] and impaired kidney function [creatinine 2.1 mg/dL (r.i. 0.67-1.17), urea 57 mg/dL (r.i. 17-49)]. Due to the worsening of clinical conditions and the renal impairment, the patient was admitted to the Nephrology department and monitored through a close and fruitful partnership between the clinicians and laboratory professionals.

Regarding respiratory symptoms, (i.e. severe dyspnea), the lung tomography scan revealed ubiquitous bilateral consolidation areas surrounded by ground glass zones. Laboratory investigations revealed increased eosinophil count (42.6%, 10.18x10^9/L), very high total IgE (6 400 UI/mL, r.v. <100 UI/mL) and serum eosinophil cationic protein (ECP, 120 µg/L, r.v. <13 µg/L)

Regarding the renal involvement, a kidney biopsy revealed a focal segmental necrotizing glomerulonephritis with half-moon structures and laboratory testing showed, as wll as high creatinine levels, proteinuria (1 397 mg/24h; r.v. <140) and haematuria (>1.0 mg/dL).

Concerning the skin of the extensive surfaces of upper and lower limbs, the patient showed pronounced papulo-erythematous purpuric lesions; a skin biopsy was performed consequently, revealing eosinophilic infiltration. The related laboratory findings highlighted very high non-specific flogosis indices and increased rheumatoid factor (71 UI/mL; r.v. <16), raising the suspicion of a systemic autoimmune pathology. The preliminary tests for detection of cryoglobulins, antinuclear autoantibodies, anticitrulline, antiphospholipids gave negative results; further laboratory investigations showed a strong positivity only to anti-neutrophil cytoplasmic antibodies (ANCA), with very high levels of anti-myeloperoxidase antibodies (anti-MPO, 740 CU/mL, r.v. <20).

Correspondig Author: Maria Rosaria De Cagna, Clinical Pathology Unit, "SS. Annunziata" Hospital, Taranto.
E-mail: mariarosaria.decagna@asl.taranto.it

Received: 28.03.2023 Revised: 19.04.2023 Accepted: 01.05.2023

Published online: 15.05.2023 DOI:10.19186/BC_2023.035

By matching clinical, instrumental and laboratory findings, the suspicion of ANCA-associated vasculitis became a confirmed diagnosis. In particular, according to the recent diagnostic criteria of the American College of Rheumatology (1), this case could be classified as a new onset of Eosinophilic Granulomatosis with Polyangiitis (EGPA), following SARS-CoV-2 vaccination. The patient was treated with metilprednisolone (3 boluses of 1 g/day), then prednisone (1 mg/kg/day) and 2 infusions of Rituximab (375 mg/m²). After two months, the follow-up tests revealed normal serum creatinine level (0.8 mg/dL), reduction of proteinuria, normalization of Anti-MPO and complete remission of the respiratory and cutaneous status.

DISCUSSION

Vaccination against SARS-CoV-2 has been crucial in the global fight against the pandemic; moreover, it has demonstrated high efficacy at preventing coronavirus disease 2019 (COVID-19) and a beneficial safety profile. However, it has also been reported that COVID-19 vaccines could represent a trigger factor for immune-mediated disease (2) although the causal relationship remains uncertain.

A growing number of reports describe the onset and recurrence of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) with the widespread use of the anti SARS-CoV-2 vaccines (3,4). Previously, numerous reports have described a temporal association of AAV to influenza vaccination (5) and, mainly, these events occurred in individuals who were susceptible to autoimmune diseases and those in remission with these disorders. Therefore, an accepted hypothesis is that AAV develops in patients with a susceptible genetic background and a simultaneous exposure to environmental or other risk factors (6), such as vaccines.

The generic term “vasculitis” defines a heterogeneous group of pathologies characterized by inflammatory and necrotizing phenomena affecting the vascular wall on histological examination. ANCA-associated vasculitis are rare systemic autoimmune diseases, predominantly affecting small and medium-sized vessels (i.e., capillaries, venules, arterioles and small arteries) of several organs, such as kidneys, lungs, and nervous system. In some instances, the diagnosis is difficult and, if the degree of organ disorder is severe, the disease becomes refractory and is associated with a poor prognosis.

The incidence is estimated at around 20-30 cases per million and it can affect individuals of any age (7), although more frequently between the fifth and seventh decade of life, without gender prevalence.

ANCA-associated vasculitis is characterized by circulating autoantibodies against cytoplasmic components of neutrophil granulocytes, in particular proteinase 3 (PR3) and myeloperoxidase (MPO) and encompass three distinct disease phenotypes: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and EGPA (formerly known as Churg-Strauss syndrome).

When there is a suspicion of AAV, the diagnostic algorithm includes, after a careful anamnesis and an accurate clinical examination, imaging and biopsy investigations (CT, X-rays, biopsies) for the evaluation of organ involvement, according to the clinical status. At the same time, a series of laboratory assays, more or less specific for a particular autoimmune pathology, has to be performed. Laboratory findings often reach the clinician before the results of biopsy or imaging tests, so a close interaction between clinicians and laboratory professionals is crucial for a fast and proper patient management.

In case of a suggestive clinical condition, the laboratory strategy for the diagnosis of a suspected AAV vasculitis is to proceed with high-quality monospecific tests for detection of anti-MPO and/or anti-PR3. A marked positivity of one of them could already be sufficient, without the need for a second monospecific method, or indirect immunofluorescence to confirm the result (8).

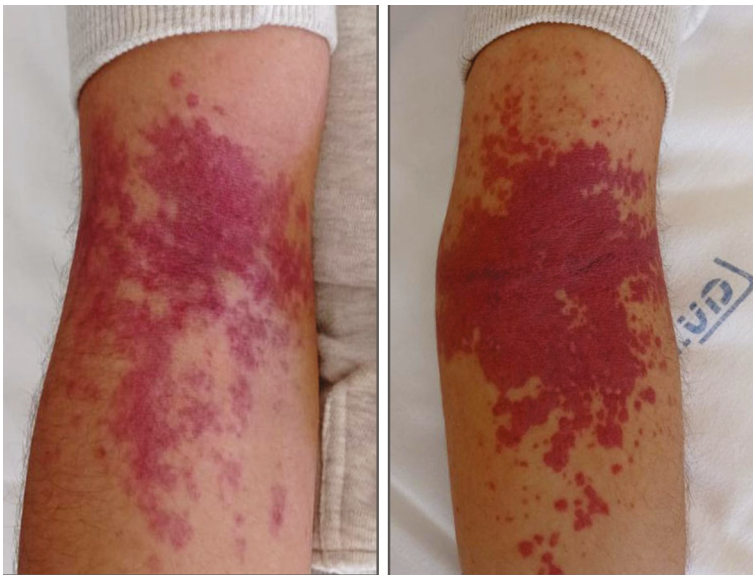

Figure 1

Edema and papulo-erythematous/purpuric lesions on limbs.

In this patient, the laboratory finding of very high levels of anti-MPO along with the evaluation of clinical situation and the imaging and biopsy led to the diagnosis of AAV.

Laboratory testing also play an important role in supporting a finer classification of AAV, according to the new criteria defined in March 2022 by the American College of Rheumatology (1). The laboratory findings for the determination of the classification score are of particular relevance: eosinophil count ≥1x10^9/L and haematuria. These criteria, along with obstructive airway disease and extravascular eosinophilic predominant inflammation, led us to conclude for a new onset of EGPA, following SARS-CoV-2 vaccination

The role of laboratory does not end with the definition of the diagnosis, but continues during the treatment and the disease monitoring. Before treatment with Rituximab and during therapy, the clinical laboratory performed flow-citometry to evaluate the B-lymphocytes status, as indicator of the effectiveness. At two months follow-up examination, laboratory assays highlighted the normalization of a number of parameters: creatinine, anti-MPO, total IgE, ECP and eosinophilic count, in agreement with the complete remission of the respiratory and cutaneous clinical status. All this confirms that a close interconnection between clinicians and laboratory is always desirable.

We have described a *de novo* case of ANCA-MPO vasculitis, with onset immediately after the administration of an anti-COVID vaccine in a man younger than those who normally develop this disease. Although a very short chronological correlation between the administration of the two doses and the outbreak of symptoms is evident, additional factors (genetic or predisposing) may have acted as trigger for the onset of the disease in this patient.

The safety and efficacy of mRNA vaccines in the prevention of COVID-19 has been widely demonstrated, however in this case environmental and genetic factors may have set the stage for the development of vasculitis, and the vaccine may have triggered a domino effect. For instance, the patient may have an HLA haplotype that correlates with the disease, which may have triggered the vaccine to induce the production of ANCA antibodies (9). On the other hands, some reports have postulated the concepts of 'molecular mimicry' or 'bystander activation of T-helper 1 autoreactive lymphocytes' as possible triggering mechanisms for autoimmune manifestations (10).

One of the major challenges of medicine is searching for tools that identify risk conditions in "apparently" healthy subjects or in patients with pathologies (specific allergies/ autoimmune diseases), who may develop complications in case of vaccination.

At the same time, patients with autoimmune diseases in remission and patients on immunosuppressive therapy should be encouraged to continue vaccination protocols with a close monitoring for the onset of specific symptoms.

CONFLICT OF INTEREST

None

REFERENCES

1. 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.
2. Talotta R. Do COVID-19 RNA-based vaccines put at risk of immune-mediated diseases? In reply to "Potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases". Clin Immunol 2021;224:108665.
3. Prabhahar A, Naidu GSRSNK, Chauhan P, Sekar A, Sharma A, Sharma A, et al. ANCA-associated vasculitis following ChAdOx1 nCoV19 vaccination: case-based review. Rheumatol Int 2022;42:749-58.
4. Bomback AS, Kudose S, D'Agati VD. De Novo and relapsing glomerular diseases after COVID-19 Vaccination: what do we know so far? Am J Kidney Dis 2021;78:477-80.
5. Watanabe T. Vasculitis following influenza vaccination: a review of the literature. Curr Rheumatol Rev 2017;13:188-96.
6. Scott J, Hartnett J, Mockler D, Little MA. Environmental risk factors associated with ANCA associated vasculitis: A systematic mapping review. Autoimmun Rev 2020;19:102660.
7. Kitching AR, Anders HJ, Basu N, Brouwer E, Gordon J, Jayne DR, et al. ANCA-associated vasculitis. Nat Rev Dis Primers 2020;6:71.
8. Bossuyt X, Cohen Tervaert JW, Arimura Y, Blockmans D, Flores-Suárez LF, Guillevin L, et al. Position paper: Revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis. Nat Rev Rheumatol 2017;13:683-92.
9. Obata S, Hidaka S, Yamano M, Yanai M, Ishioka K, Kobayashi S. MPO-ANCA-associated vasculitis after the Pfizer/BioNTech SARS-CoV-2 vaccination. Clin Kidney J 2021;15:357-9.
10. Costanzo G, Ledda AG, Ghisu A, Vacca M, Firinu D, Del Giacco S. Eosinophilic granulomatosis with polyangiitis relapse after COVID-19 vaccination: a case report. Vaccines (Basel) 2021;10:13.