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RESEARCH ARTICLE

CYTOKINE STORM 15 DAYS AFTER VIRAL-INDUCED VACCINE, MACROPHAGIC ACTIVATION SYNDROME OR VACCINE-INDUCED IMMUNE THROMBOCYTOPENIA (VITT) SYNDROME?

H. Ziani, A. Azzouzi, A. Elhijri and R. Elmoussaoui

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Abstract

Vaccination is considered the most promising approach to ending or containing the 2019 coronavirus (COVID-19) pandemic. Available vaccines have proven to be very safe and effective. Nevertheless, post vaccination complications have been described.

We report the case of a 26-year-old female patient admitted for management of severe viral pneumonitis due to SARS COV2, 15 days after the 1st dose of the vaccine, whose investigations suggest a macrophagic activation syndrome or vaccine-induced immune thrombocytopenia syndrome (VITT)

Macrophagic activation syndrome (MAS) is observed in a multitude of clinical situations encountered in adults. It is characterized by a series of non-specific clinical and biological signs, the combination of which should raise the suspicion of the diagnosis and lead to a cytological or histological examination to confirm it. Its occurrence requires a fairly exhaustive etiological work-up. It is a serious pathology, with a severe prognosis and a poorly codified treatment [1, 2].The objective of our work is to report a case of MAS strongly suspected following an infection due to COVID in a young 26 year old patient, 15 days after the 1st dose of the vaccine, a Vaccine-induced Thrombotic Thrombocytopenia (VITT) not to be eliminated either.

Introduction:-

SARS-Cov2 is a new bread of the coronavirus responsible of the COVID19 world pandemic. This infection is responsible for an exacerbated inflammatory response, characterized by a massive release of pro-inflammatory cytokines (IL-1, IL-6, IL-10, IL-18, IFN-gamma, TNF-alfa) leading to a "cytokine storm" that seems to be behind the development of acute respiratory distress syndrome and severe multivisceral failures. Various autoimmune and autoinflammatory manifestations have beenlinked to COVID-19 infections, some of which have some similarities with macrophagic activation syndrome. However, the mechanisms involved in the occurrence of these manifestations remain unknown.

Case Report:-

This is a young 26 year old patient, without any history or risk factor, who developed a typical Covid pneumopathy picture 15 days after receiving the first dose of the vaccine (AstraZenecca): Flu syndrome, headache, fever without alteration of the general state and stable on the respiratory level: FR at 16c/min and SaO2 at room air at 99%

Corresponding Author:- H. Ziani

motivating the realization of an antigenic PCR test returned positive from where the therapeutic protocol was administered at home.

5 days later, the patient presented a respiratory discomfort of rapid aggravation motivating her admission to the Central Intensive Care Unit in Rabat, Examination objectified a tachypneic patient at 50 c/min, room air SaO2 at 60% and 75% under MHC (15l/min), weak thoracic ampliation and altered ventilatory mechanics, HR at 130 b/m, BP = 10/5.

A thoracic CT scan was performed showing images in favor of a severe pneumopathy due to SARS-COV2 with aspect of bacterial superinfection without sign of massive pulmonary embolism. After launching the complete blood work, the patient was put under NIV in DV position for possible oxygenation and recruitment of the condensed areas but without improvement indicating the implementation of an artificial ventilation.

The biological workup showed: Hb level at 6g/dl, platelets at 84000, Polynuclear lymphocytes at 400 Elements/ul, Serritinemia at 898 ng/ml and LDH at 487 u/l, fibrinogen at 0.5 g/liter, CRP at 420 compared to 350 12 hours before, procalcitonin negative at 0.2ng/ml, PaO2 at 48mmHg under 100% FiO2.

In view of this clinical and biological picture and the delay of appearance after the vaccine, MAS was suspected in the 1st stage and the patient was put on a full dose of methyliprednisolone, a VITT in the 2nd stage, the evolution was marked by a rapid aggravation and a mutlivisceral failure refractory to the therapeutic means, the patient died after 36h of her admission.

NB: HIV serology performed returned negative.

Discussion:-

MAS is a multisystemic disease, related to an intense activation of the immune system, corresponding to a more or less diffuse infiltration of tissues by activated macrophages responsible for a situation known as Cytokine Storm. It belongs to the group of non-langerhansian and non-malignant histiocytoses[3]. This syndrome was first described in 1939 by Scott and Robb-Smith in adults as a neoplastic proliferation of histiocytes. The mechanisms explaining MAS are not completely elucidated, but recent advances in the genetic study of familial forms, with the discovery of the responsible genes, have completely changed the understanding of its pathophysiology [4, 5]. Epidemiologically, pediatric forms are often better documented and the overall incidence of the different types of HL is of the order of 1 case per million in children [6, 7].

Clinically, the manifestations are not very specific and it is their association that should lead to the diagnosis. At present, the Henter criteria are the accepted diagnostic criteria for MAS, and the diagnosis of MAS is made when five of eight criteria are present: fever, splenomegaly, cytopenia (hemoglobin (Hb) < 9 g/dl, platelets < 100,000/mm3, neutrophils < 1,000/mm3), hypertriglyceridemia (> 3 mmol/l) and/or hypofibrinemia (< 1.5 G/l), marrow hemophagocytosis (or other tissue: lymph node, spleen, etc.), ferritin > 500 mg/l, soluble CD25 > 2400 U/ml and no or low natural killer (NK) activity [7, 8].

Other signs may be found depending on the case, which may be of major etiological significance, in particular neurological signs such as irritability, mental confusion, ataxia, visual disturbances, and convulsive seizures. These neurological disorders can be letal. The etiological investigation of suspected MAS must be exhaustive, and the clinical picture is often dominated by the signs of the causal disease. The pathological situations associated with the occurrence of a hemophagocytic syndrome are diverse, most often marked by an underlying "dysimmune" state.

There are 2 forms of MAS: primary and hereditary forms: represented mainly by familial or sporadic hemophagocytic lymphohistiocytosis occurring in childhood, in addition to other primary causes: Griscelli syndrome, Chediak-Hegachi syndrome and Purtilo syndrome. These hereditary immune system disorders are characterized by macrophagic and T-cell lymphocytic activation called hemophagocytic lymphohistiocytosis (or accelerated phase of the disease), often triggered by an intercurrent intracellular germ infection (most often viral); secondary forms are usually associated with malignancy, autoimmune disease, infectious disease, or immunosuppressive therapies. In clinical practice, this distinction is very difficult and can only be judged on the evolution of the patient under treatment. Thus, the identification of a potentially responsible infection does not rule

out the diagnosis of primary MAS, which may itself be triggered by such an event [8, 9]. The last element that supported our diagnostic hypothesis was the concomitant existence of a viral infection.

In late February 2021, a prothrombotic syndrome was observed in a small number of individuals who received ChAdOx1 CoV-19 vaccine (AstraZeneca, University of Oxford and Serum Institute of India), an adenoviral vector-based vaccine. Subsequently, similar results were observed in a small number of individuals who received the Ad26.COV2.S vaccine (Janssen; Johnson & Johnson), also based on an adenoviral vector. This syndrome has been called Vaccine-induced Thrombotic Thrombocytopenia(VITT). It has also been called thrombosis with thrombocytopenia syndrome (TTS) and vaccine-induced immune thrombocytopenia (VIPIT). This diagnosis can be evoked also in our reported case.

VITT is caused by antibodies that recognize platelet factor 4 (PF4, also called CXCL4) bound to platelets. These antibodies are immunoglobulin G (IgG) molecules that activate platelets via low-affinity platelet FcγRIIa receptors (receptors on the surface of platelets that bind to the Fc portion of IgG).

Ultimately, platelet activation (and possibly activation of other cells such as neutrophils) results in marked stimulation of the coagulation system and clinically significant thromboembolic complications.

Thrombosis in VITT can occur in typical sites of venous thromboembolism such as pulmonary embolism (PE) or deep vein thrombosis (DVT) in the leg [11]; however, a distinguishing feature of the syndrome is thrombosis in unusual sites, including splanchnic veins (splenic, portal, mesenteric), adrenal veins (risk of adrenal insufficiency), and cerebral and ophthalmic veins. Arterial thrombosis, including ischemic stroke (often middle cerebral artery) and peripheral arterial occlusion have also occurred, often in individuals with venous thrombosis.

The pathophysiologic explanation for these unusual sites of thrombosis is unknown. The distribution is similar to that seen with other unusual thrombophilias such as paroxysmal nocturnal hemoglobinuria (PNH) and thromboembolic complications associated with a JAK2 mutation. Autopsy studies in decedents with VITT have demonstrated catastrophic venous thrombosis involving multiple large and small vessels [16].

-This syndrome can be triggered in medical patients, usually following a viral or bacterial infection, although sometimes no previous trigger is identified, or by an adenoviral vector COVID-19 vaccine.

The syndrome likely begins within a narrow window 5-10 days after vaccination, leading to identification of cases usually between 5 and 30 days after vaccination (potentially later, especially if there is a delay in recognition of symptoms and/or seeking medical attention) [15].

Several reports have also described a general flu-like syndrome within the same 5- to 10-day window or at the time of thrombosis presentation, perhaps suggesting an enhanced inflammatory response [12,13 ,14].As awareness of the syndrome has increased, less typical presentations have emerged, such as thrombosis without thrombocytopenia or thrombocytopenia without thrombosis.

In a series of 220 patients with definite or probable VITT, the following characteristics were noted [16]:
-Age - Median 48 years, range 18 to 79 years.
-Sex - 55 percent female, 45 percent male.
-Time since vaccination - Median 14 days; range 5 to 48 days.
-Platelet count - Median 47,000/microL, range 6,000 to 344,000/microL.
-Fibrinogen - Median 2.2 g/L (220 mg/dL), range 0.3 to 4.4 mg/dL.
-D-dimer - Median 24,000 fibrin equivalent units (FEU; equivalent to 12,000 ng/mL), range 5,000 to 80,000 FEU.

This syndrome can be complicated by sudden death (diagnosis of VITT established postmortem) which may reflect a number of thrombotic complications including coronary thrombosis, pulmonary embolism, or intracerebral hemorrhage[12].

Conclusion:-

The pandemic of COVID 19 is still being explored, several hypotheses and theories are involved in the pathophysiology of the severe forms, of which the macrophagic activation syndrome is one of these hypothesis

correlated with the cytokine storm and seen in quite a few patients, The genetic exploration and early diagnosis of this syndrome may improve the management of COVID 19 pneumopathy, the second hypothesis which is under research and Vaccine Induced Thrombotic Immune Thrombocytopenia (VITT).

References:-

1 -Berrady R, Bono W. Le syndrome d'activation lympho-histiocytaire (SALH) Annales Françaises d'Anesthésie et de Réanimation. 2014;33(1):26–32. [PubMed] [Google Scholar]
2 -George Melissa R. Hemophagocytic lymphohistiocytosis: review of etiologies and management. Journal of Blood Medicine. 2014;5:62–86. [Article PMC gratuit] [PubMed] [Google Scholar]
3 -Arico M, Danesino C, Pende D, Moretta L. Pathogenesis of haemophagocyticlymphohistiocytosis. Br J Haematol. 2001;114(4):761–769. [PubMed] [Google Scholar]
4 -Henter JI, Elinder G, Ost A. Diagnostic guidelines for hemophagocytic lymphohistiocytosis: The FHL study group of the Histiocyte society. Semin Oncol. 1991;18(1):29–33. [PubMed] [Google Scholar]
5 -Scott RB, Robb-Smith HT. Histiocytic medullary reticulosis. Lancet. 1939;234(6047):171–236.[Google Scholar]
6 -Arico M, Danesino C, Pende D, Moretta L. Pathogenesis of haemophagocyticlymphohistiocytosis. Br J Haematol. 2001;114(4):761–769. [PubMed] [Google Scholar]
7 -Henter JI, Elinder G, Ost A. Diagnostic guidelines for hemophagocytic lymphohistiocytosis: The FHL study group of the Histiocyte society. Semin Oncol. 1991;18(1):29–33. [PubMed] [Google Scholar]
8 -Henter JI, Elinder G, Soder O, Ost A. Incidence in Sweden and clinical features of familial hemophagocytic lymphohistiocytosis. Acta Paediatr Scand. 1991;80(4):428–435. [PubMed] [Google Scholar]
9 -Janka GE. Hemophagocytic syndromes. Blood Rev. 2007;21(5):245–53. [PubMed] [Google Scholar]
10 -Karrasa, Thaunato, Noëll H, Delahousse M. Flammarion médecine-sciences Actualités néphrologiques. 2005. syndrome d'activation macrophagique: implications pour le néphrologue. [Google Scholar]
11 -Gabarin N, Patterson S, Pai M, et al. Venous Thromboembolism and Mild Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination. ThrombHaemost 2021.
12-Greinacher A, Thiele T, Warkentin TE, et al. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. N Engl J Med 2021; 384:2092.
13-Bayas A, Menacher M, Christ M, et al. Bilateral superior ophthalmic vein thrombosis, ischaemic stroke, and immune thrombocytopenia after ChAdOx1 nCoV-19 vaccination. Lancet 2021; 397:e11.
14-Muir KL, Kallam A, Koepsell SA, Gundabolu K. Thrombotic Thrombocytopenia after Ad26.COV2.S Vaccination. N Engl J Med 2021; 384:1964.
15- Pishko AM, Cuker A. Thrombosis After Vaccination With Messenger RNA-1273: Is This Vaccine-Induced Thrombosis and Thrombocytopenia or Thrombosis With Thrombocytopenia Syndrome? Ann Intern Med 2021.
16- Pomara C, Sessa F, Ciaccio M, et al. Post-mortem findings in vaccine-induced thrombotic thombocytopenia. Haematologica 2021; 106:2291.