Autoimmune/inflammatory syndrome leading to macrophage activation syndrome: an example of autoinflammatory spectrum disorder?

To the Editor:

A 14 month old previously healthy girl was admitted to the hospital because of long-lasting (14 days) fever with rash that appeared 3 days after the vaccination with MMR (measles, mumps, and rubella). Laboratory tests revealed an increased number of white blood cells (23 K/µl), elevated C-reactive protein (27 mg/L) and anemia (hemoglobin 7.9 g/dl). Chest X-ray demonstrated interstitial infiltration, while ultrasound examination of the abdomen and heart echocardiography were normal. Viral (Epstein-Barr virus, cytomegalovirus, PV-B19, hepatitis C and B viruses, human immunodeficiency virus) and atypical bacterial (*Mycoplasma*, *Borrelia*) infections were ruled out. Blood culture was negative. Despite broad-spectrum antibiotics, the girl was febrile, rash and lymphadenopathy were noted, and during the course of the disease parameters of inflammation increased. Atypical Kawasaki disease was suspected, the treatment with intravenous immunoglobulin (IVIG) and aspirin was started but the rash persisted and became polymorphic and generalized. Steroids were introduced resulting in rapid clinical improvement. The steroids were discontinued, but 3 weeks later the girl was again admitted to the hospital, presenting with fever, arthritis, generalized rash, hepatosplenomegaly and cervical lymphadenopathy. Markers of inflammation were present, and a decrease in white blood cell and platelet count was observed; ferritin was markedly elevated (150,000 ng/ml) and hypofibrinogenemia was noted. Antinuclear antibodies were negative. Blood smear revealed single macrophages. The girl was suspected of having macrophage activation syndrome. High dose steroids, cyclosporine A (CyA) and antibiotics were given with partial response. Kawasaki-like symptoms were present after 10 days (fever, red lips, "strawberry tongue," generalized erythema with subcutaneous edema, desquamation of the fingers). IVIG and aspirin were once again administered and steroids and CyA were continued, resulting in full recovery.

A working diagnosis of ASIA (autoimmune/auto-inflammatory syndrome induced by adjuvants; here, MMR vaccine was an adjuvant) complicated by macrophage activation syndrome (MAS) was made. To the best of our knowledge this association has not been reported before. Both MAS and ASIA, which are immune mediated conditions, have been described separately in the medical literature.

MAS is a severe, potentially life-threatening hyperinflammatory condition that usually appears as a complication of rheumatic diseases (it occurs most commonly in systemic onset juvenile idiopathic arthritis, so-JIA). Masters et al. [1] classified MAS as an autoinflammatory disorder, "truly leading to a horror autoinflammaticus." It is caused by the activation and uncontrolled proliferation of T lymphocytes and macrophages leading to cytokine overproduction. MAS is a form of secondary hemophagocytic lymphohistiocytosis (HLH) (current data suggest a fundamental pathophysiological relationship between primary HLH and MAS) and this is why many clinicians use criteria of the Histiocyte Society [2]. Recently, Ravelli et al. [3] proposed new criteria for children with so-JIA. MAS could be triggered by many factors, especially infections (particularly viral), but it could also be related to the flare of autoimmune disease (as a first manifestation of the disease, or in the further clinical course) with or without an infectious trigger. It is characterized by unremitting fever, cytopenias, liver dysfunction, coagulopathy, hyperferritinemia and hypofibrinogenemia. The treatment consists of combined immunosuppressive drugs. Any delay in therapy may lead to irreversible multi-organ failure.

In 2011 a new entity termed ASIA was described by Shoenfeld and Agmon-Levin [4]. It belongs to the spectrum of immune mediated diseases triggered by an adjuvant stimulus such as chronic exposure to silicone, tetramethylpentadecanem prosane, aluminium and other adjuvants found in vaccines. It is hypothesized that a genetic background plays a key role in the appearance of vaccine-related disease. It remains to be defined whether the pathogenic pathway responsible for this syndrome is common to all adjuvants or whether specific pathways exist for different adjuvants. The adjuvants impinge on both the innate and adaptive syndrome. Its effect on the adaptive immune response is mediated through activation of the NALP3 inflammasome, macrophages, lymphocytes and dendritic cells. Diagnostic criteria were proposed by Shoenfeld. In our patient, exposure to vaccine, the appearance of pyrexia, dry mouth and arthralgia, and suspicion of autoimmune disease (vasculitis) were noted.

The patient did not fulfil the classification criteria of any well-defined connective tissue disorder. Infections and malignancies were also ruled out. It is worth emphasizing that MAS/ASIA could be the first manifestation of rheumatic disease. Diagnostic difficulties in this case result from overlapping clinical syndromes such as MAS, ASIA, so-JIA, and Kawasaki disease; thus we hypothesized that these conditions are different phenotypes of undefined immunodeficiency syndrome (polygenic inflammasonopathy? autoinflammatory spectrum disorder?). We suppose that MAS could be regarded as an end stage of immunodysregulation in ASIA. Kawasaki-like disease in our patient would suggest undefined vasculitis, periodic fever syndrome, the first manifestation of so-JIA triggered by vaccination, or a new autoinflammatory disease entity, but further clinical observation is required to verify the final diagnosis.

Molecular tests in our patient are pending. Until we have the results of genetic tests the above statements could be regarded as speculative. The authors are aware that the diagnosis of ASIA complicated by MAS is preliminary and that other conditions that can present in this manner have to be excluded, e.g., genetic forms of HLH and periodic fever syndromes. It should be noted that the genetic condition caused by mutations in NLRC4 could be related to MAS. It is associated with very high IL-18 levels even

when patients are clinically inactive, and patients have no NK cell defect, suggesting that MAS and HLH differ in triggering a common end-pathway that is interferon-gamma driven. Testing for serial ferritin and IL-18 levels (not done in our patient) would be helpful to add this case report to our current understanding of MAS.

The vaccination could simply represent a trigger in a patient genetically predisposed to develop a MAS; nevertheless, in this case, the possible harmful role of vaccination without a complete and reliable search for other possible causes should be considered very carefully.

Further research is warranted to identify pathomechanisms and expand diagnostic methods in patients with ASIA/MAS/HLH using detailed genetic and functional studies that enable a more accurate understanding of the essence of these conditions. Studies evaluating the impact of therapy (such as widely used monoclonal antibodies) on the clinical course and the choice of optimal treatment are of importance. Above all, identifying individuals at higher risk of adverse reaction due to vaccination owing to his or her specific genetic background is needed to avoid possible serious adverse reactions.

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