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Clinical Insights

Thrombosis with Thrombocytopenia Syndrome associated with viral vector COVID-19 vaccines

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On March 11 2021, the European Medical Agency highlighted two relevant issues, after the decision by the Danish Health Authority to temporarily suspend its vaccination campaign with Vaxzevria (the COVID-19 vaccine by AstraZeneca) following the reports of thromboembolic events (TE) associated with the administration of the vaccine: 1) lack of evidence of a cause/effect relationship between the vaccine and TE; 2) the number of reported TE (30 in around 5,000,000 vaccinated people) was no higher than that expected [1]. However, the real essence of the problem emerged about a week later: it was not the number of TE that was of concern, but, rather, their unusual nature: the affected patients were all young (<50 years old) and previously healthy, they displayed widespread thrombi, predominantly in unusual sites, and also had thrombocytopenia [2]. These data suggested that a new syndrome had emerged, which is termed "Thrombosis with Thrombocytopenia Syndrome (TTS)". I think that the two alternative definitions of the syndrome, "vaccine-induced prothrombotic immune thrombocytopenia (VIPIT)" and "vaccine-induced immune thrombotic thrombocytopenia (VITT)", should be dismissed for two reasons: 1) the cause-effect relationship with vaccination has not yet been unequivocally established; 2) the general reference to "vaccine" is not justified, as the syndrome has been observed only in association with 2 particular COVID-19 vaccines.

The association of thrombosis and thrombocytopenia had been previously observed in patients with Heparin-Induced Thrombocytopenia (HIT), an immune prothrombotic disorder caused by antibodies directed against multimolecular complexes of polyanionic heparin and cationic platelet factor 4 (PF4), which activate platelets through their Fc receptor [3]. A combination of thrombocytopenia and thrombosis has also been observed in a similar syndrome affecting patients not treated with heparin, in which the PF4 binding function of heparin is taken over by other polyanions, such as condroitinsulfate, nucleic acids, polyphosphates or bacterial components: this HIT-like syndrome is termed autoimmune HIT [4]. Antibodies against polyanions/PF4 can be assessed by immunoassays, such as enzyme-linked immunosorbent assay (ELISA) and chemiluminescent immunoassay (CLIA). In case of positivity of these relatively unspecific screening tests, the diagnosis of classical HIT relies on confirmatory tests of activation of normal platelets by patients' sera, which, in the case of classical HIT activate platelets in presence of pharmacological concentrations of heparin (0.2 IU/mL), but not in the absence of heparin or in presence or very high heparin concentrations (100 IU/mL); in contrast, sera of autoimmune HIT may activate platelets also in the absence of heparin [4].

Clinical and laboratory features of TTS

It has recently been demonstrated that TTS is a (sub)type of autoimmune HIT, as it is characterized by positivity of the screening tests for antibodies against polyanions/PF4 [5-8, Scavone M et al. unpublished observations]. It is important to note that only the very unspecific ELISA test gives positive results in TTS, while the CLIA test gives negative results [8]. Sera from TTS patients behave very erratically in the HIT

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