An idiotypic network dysregulation could be related to the pathogenesis of vaccine-induced immune thrombotic thrombocytopenia (VITT) following vaccination with vaccines expressing Spike protein of SARS CoV2

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Dear Editor,

ChAdOx1 nCov-19 (Oxford–AstraZeneca), Ad26.COV2.S (Johnson & Johnson/Janssen), mRNA-1273 (Moderna) and BNT16b2 (BioNTech-Pfizer) are vaccines for preventing coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). ChAdOx1 nCov-19 is made up of a recombinant chimpanzee adenoviral vector and Ad26.COV2.S of a recombinant adenovirus type 26, modified to contain the gene for making the protein of Spike (S protein) structure from SARS-CoV-2. mRNA-1273 and BNT16b2 are RNA vaccines that use the cellular machinery to produce the Spike protein and make the immune system recognize it and generate neutralizing antibodies against the virus [1]

Here, we propose a possible complementary pathophysiological pathway that could explain VITT: S protein is composed of two subunits (S1 and S2). The S1 subunit is the immunodominant antigen during infections due to its accessibility for immunological recognition and S2 subunit has a receptor-binding domain (RBD) which joins to the receptor from the host, the dimeric human angiotensin-converting enzyme 2 (ACE2) widely expressed in respiratory epithelial cells. Human platelets also exhibit ACE2 expression [3]

After vaccination an idiotypic/anti-idiotypic network dysregulation could occur, with the subsequent development of epitopes with the same sequence of the S protein. Fab fragment of these antibodies could bind to the ACE2 receptor and trigger thrombotic phenomena associated with downregulation of this receptor. It increases angiotensin II levels and its consequent activating effect on coagulation, mediated among other mechanisms by tissue factor (TF) activation. Platelets may also be targeted by the presence of those autoantibodies, causing both promoting their activation and destruction.

In 1974, the Nobel Prize in Medicine, Niels Jerne, planted the later confirmed hypothesis of the immunological network. In this postulate, the existence of idiotype and anti-idiotype antibodies is proposed. Idiotype antibody is defined as a group of antibodies with the same antigenic binding group (complementarity determining regions—CDR) of single clonality. Anti-idiotype antibodies are those that recognize the CDR of another antibody. The idiotype/anti-idiotype network has multiple implications including autoimmunity regulation neutralizing pathogenic idiotype antibodies, basis for immunotherapies which have been called cancer vaccines, and role pathogenic in autoimmunity due to its dysregulation, among other.

It has been postulated that the idiotype/anti-idiotype network may be related to the immune response in Covid-19
and its vaccines [4]. Vaccines encoding the full-length wild-type SARS-CoV-2 S protein and induce an immune response that includes antibodies directed against the RBD of the S protein (idiotype). The RBD situated in the S1 dominion of the S protein can bind to cell receptor ACE2. Due to dysregulation of the immune network, antibodies are subsequently generated against the antibody directed to the RBD (anti-idiotype). Due to the complementarity, these antibodies finally would express the same antigenic configuration of the S protein in their variable region. Anti-idiotype with amino acid sequences shared with S protein would bind to ACE-receptor producing its downregulation and increasing angiotensin II levels. This protein is associated with endothelial damage and thrombotic phenomena due to activation of TF. Anti-idiotype fragments in circulation theoretically would have the ability to bind directly to ACE2 in platelets and contribute to its destruction (autoimmune thrombocytopenia). Platelets are also activated, facilitating the release of coagulation factors, secretion of inflammatory factors, and leukocyte–platelet aggregates, which can contribute to the hypercoagulation and formation of thrombi.

This was demonstrated by Arthur et al. who evidenced the presence of antibodies against ACE2 in patients with SARS COV2 infection [5]. VITT could then have an autoimmune basis in susceptible patients, where an idiotypic network dysregulation could be present. The way the S protein is presented to the host’s immune system through adenovirus viral vectors may contribute to the development of these events.

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**Declarations**

**Conflict of interest** The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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**Informed consent** Not required.

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