Editorial

Capillary leak syndrome in COVID-19 and post COVID-19 vaccines

Luca Roncati1,*, Greta Gianotti1, Elisa Ambrogi1, Giovanna Attolini1

1 Department of Surgery, Medicine, Dentistry and Morphological Sciences with interest in Transplantation, Oncology and Regenerative Medicine, University of Modena and Reggio Emilia, 41124 Modena, Italy

*Correspondence: luca.roncati@unimore.it; roncati.luca@aou.mo.it; emailmedical@gmail.com (Luca Roncati)

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Coronavirus Disease 2019 (COVID-19) is the most dramatic pandemic of the new millennium with repercussions also in the gynaecological oncology field [1–3]. The cervical cancer screening and the management of gynaecological tumors have been negatively impacted by COVID-19, with many interventions delayed or postponed [4]. Once infected, oncological patients are in addition at a higher risk of developing a severe form of the disease, due to chemotherapy and immunocompromise [5, 6]. To counteract all this, specific vaccines have been launched in record time under emergency use authorization or conditional marketing authorization [7]; however, very rare neurological (Guillain–Barré syndrome) and thrombotic events after Vaxzevria® (formerly COVID-19 Vaccine AstraZeneca) or COVID-19 Vaccine Janssen have caused a stir in the scientific community and public opinion [7]. If Guillain–Barré syndrome is a known possible adverse reaction to vaccination, in which the immune system mistakenly attacks and damages peripheral nerves’ myelin [8–10], for thrombotic events the matter is quite different. In fact, these severe, even fatal, thrombotic events have been only recently traced back to autoimmune thrombocytopenia mediated by platelet-activating antibodies against platelet factor 4, which clinically mimics autoimmune heparin-induced thrombocytopenia [11–13]. Therefore, the European Medicines Agency (EMA) has updated the product information of both the vaccines in the midst of vaccination campaign, as follows:

“thrombosis with thrombocytopenia syndrome, in some cases accompanied by bleeding, has been observed very rarely following vaccination with Vaxzevria®. This includes severe cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia. Some cases had a fatal outcome. The majority of these cases occurred within the first three weeks following vaccination and occurred mostly in women under 60 years of age” and “a combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with COVID-19 Vaccine Janssen. This includes severe cases of venous thrombosis at unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis as well as arterial thrombosis concomitant with thrombocytopenia. Fatal outcome has been reported. These cases occurred within the first three weeks following vaccination, and mostly in women under 60 years of age” [14, 15].

More recently, EMA’s safety committee has reviewed six cases and three cases of Capillary Leak Syndrome (CLS) in people who had received Vaxzevria® and COVID-19 Vaccine Janssen, respectively. Most of the cases occurred in women and within four days from vaccination; four of those affected had a CLS history and three of them subsequently died [16, 17]. But what exactly is CLS? It represents a serious and temporary (1–3 days) capillary disfunction typically of the middle-aged adults characterized by hyperpermeability, maybe related to proinflammatory mediators, in which blood plasma escapes from the circulatory system into interstitial compartment, surrounding tissues or body cavities, up to 70% of total plasma volume [18, 19]. The extravasation in the extremities is so massive to cause generalized edema with rapid weight gain, hypotension, hypoconcentration, hypoaalbuminemia, and compartment syndromes, accompanied by lipothyemia or syncope and flu-like symptoms (Fig. 1); preserved consciousness, despite severe attack, is an additional and intriguing clinical manifestation often reported during episodes at hospital admission [20]. Death may occur for hypovolemic shock, arrhythmia, multiple organ failure, recovery-phase pulmonary edema, or ischemia-reperfusion injuries [20]. Moreover, in approximately four fifths of cases, a paraproteinemia is found as the expression of an underlying monoclonal gammopathy of unknown significance [18–20]. There is a primary form of CLS, also called Clarkson’s disease (from the physicians Bayard D. Clarkson who first described it in 1960) [21], and a secondary form, due to ovarian hyperstimulation, differentiation syndrome, drugs (e.g., gemcitabine and tagraxofusp), sepsis, systemic inflammatory response syndrome, autoimmune diseases, hemophagocytic lymphohistiocytosis, engraftment syndrome, anaphy-
CLS is more common in middle-aged women. CLS can be a serious complication of COVID-19 and an adverse event of COVID-19 vaccines. CLS classically occurs with a triad of signs: hypotension (<90 mmHg), hypalbuminemia (<3 g/dL), and hemocrit >43% in women, >49% in men. Patients affected by CLS experience a rapid weight gain up to 10 Kg in a couple of days. Paraproteinemia is detected in about 80% of cases. Attack therapy is nowadays based on high doses of IVIG (1g/Kg/day per 2 days). Maintenance therapy exploits low doses of IVIG (1g/Kg/month) or Montelukast, Terbutaline, and/or Theophylline with variable dosages depending on the single patient.

**Author contributions**

LR conceived, designed, and supervised the study, interpreted the data, prepared the figure with the related legend, and wrote the manuscript; GG analyzed the data; EA and GA performed the literature search. All authors read and approved the final version of the manuscript.

**Ethics approval and consent to participate**

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**References**


