PR3-ANCA vasculitis as manifestation of ASIA syndrome following aesthetic breast augmentation: a new kid on the block?

Sirs,

Granulomatosis with polyangiitis (GPA) is a small-vessel necrotising vasculitis associated with the anti-neutrophil cytoplasmic antibodies (ANCA) (1), affecting various organs including breasts. GPA is believed to be triggered in genetically predisposed people by diverse stimuli, however, we found no report of silicone-induced GPA with breast involvement. Here, we describe a case of GPA in young female with silicone breast implants presenting five weeks after COVID-19 vaccination.

A thirty-five years old female without chronic diseases, active smoker presented to the rheumatology clinic with a two-month history of right breast painful swelling, diffuse arthralgias, myalgias and elevated inflammatory markers (ESR 120 mm/hour (n.v. <15 mm/h), CRP 88 mg/L (n.v. <5 mg/L), white blood cell count 11.45 (n.v. 4.0-10.0-10^9/L)). At the age of 32 she underwent a cosmetic breast augmentation with bilateral Mentor round gel implants. Five weeks prior to her first GPA symptoms, she received the second dose of AstraZeneca Oxford SARS-CoV-2 vaccine. She denied taking regular medications or illegal substances. At admission, the patient appeared pale and in distress due to severe myalgia. The right upper breast quadrant was swollen, without accompanied redness and fever. In the following days, she progressively developed arthritis, painful paresthesias, left foot drop and finger ischaemia (Fig. 1A) leading to gangrene of distal left fifth finger (Fig. 1B). Nerve conduction study confirmed mononeuritis multiplex. Finally, nephritic urine sediment developed (glomerular erythruria, proteinuria 770 mg/day, cylindruria), however renal function remained stable. Among the immunoserological testing, cANCA, anti-proteinase 3 antibodies were present. Breast MRI revealed a concentric subcapsular thickening of the right breast without an implant rupture. Treatment with high dose steroids, hyper immune gammaglobu-

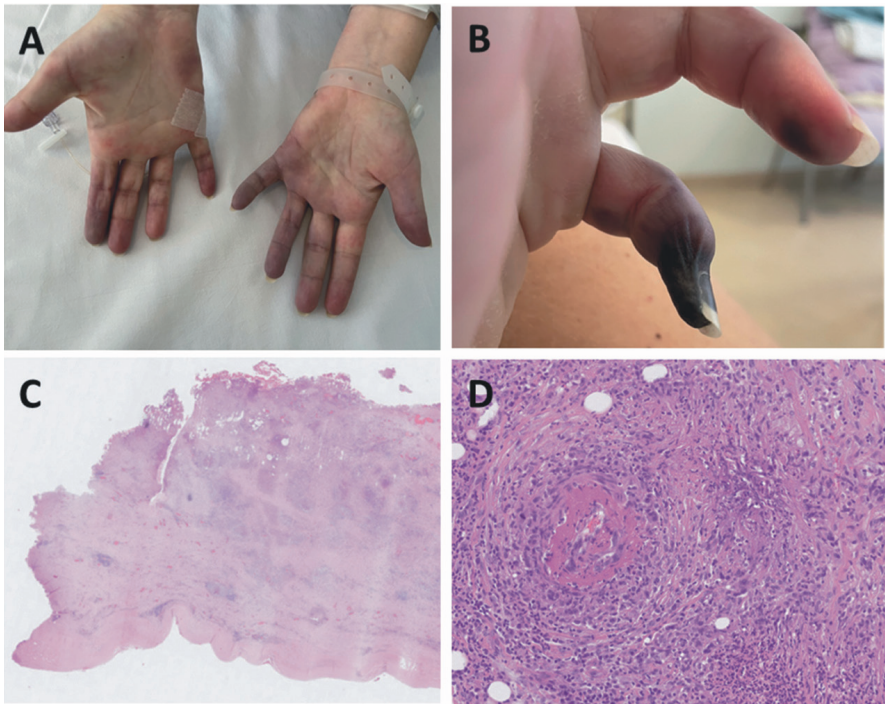

Fig. 1. A) Peripheral cyanosis of both hands with underlying capillarities; **B)** Critical ischaemia of the V distal phalanx on left hand; **C)** Histopathological examination of silicone implant capsule revealed thickened fibrous capsule with an irregular, but fairly prominent inflammatory infiltrate (scanning magnification); **D)** Multiple areas of well-formed palisading necrobiotic granulomas with a central necrosis/necrobiosis (arrows) composed of a variety of different inflammatory cells, including neutrophils, epithelioid macrophages, plasma cells and focally eosinophilic granulocytes. In the vessel walls fibrinoid necrosis along with a lymphocytic and macrophagic infiltrate was present. No foreign particles with silicone droplets evident in either of the capsules indicate no evidence of silicone leak. Special histochemical stains for bacteria (Brown and Brenn), fungi (Grocott) and mycobacteria (Ziehl-Neelsen and Auramin-Rhodamine) were negative.

Table I. Literature review of ANCA-associated vasculitis associated with breast implantation.

Publication	Systemic exposure to silicone	Local breast reaction	Type of vasculitis	Time to vasculitis onset from surgery	Vasculitis symptoms	Treatment	Associated complications
Iyoda *et al*., 2005 (7)	no signs of rupture of the envelope	purpuric rash around her breast	MPO -ANCA	30	acute progressive renal failure, pulmonary haemorrhage	high-dose steroids and plasma exchange	died of progressive pulmonary haemorrhage and multiple cerebral haemorrhage.
Kotton *et al*., 2012 (3)	no	no	Wegener, MPO antibodies	23	uveitis and pulmonary haemorrhage with respiratory failure	azathioprine and trimethoprim–sulfamethoxazole	Breast implant–associated angiosarcoma with pulmonary metastases alongside invasive pulmonary aspergillosis.
Tan *et al*., 2014 (8)	No	NA	MPO-ANCA, MPA	2	acute progressive renal failure, haematuria, pulmonary haemorrhage, and positivity	high dose steroids, cyclophosphamide, and plasmapheresis	NA
Carrera *et al*., 2021 (9)	Yes (implant rupture 3 years after surgery)	NA	MPO-ANCA	NA	Kidney failure, pleuritic effusions, alveolar haemorrage	methylprednisolone pulses, rituximab and plasmapheresis. Cyclophosphamide	SSc 1 year after implant rupture

NA: not applicable; MPO: mieloperoxidase; MPA: microscopic polyangiitis; SSc: systemic sclerosis.

lins was started along with vasodilators, low-molecular-weight heparin, and surgical explantation of breast implants was performed. Histological examination revealed fibrous capsule (Fig. 1C) bilaterally, with the presence of granulomatous necrotising vasculitis with an intense fibrinoid necrosis of vessel walls (Fig. 1D). After the surgery immunomodulatory treatment was intensified, and the patient received cyclophosphamide pulse and rituximab.

Different triggers might predispose development of autoimmune process in breast tissue, among them adjuvants, such as silicone implants, take the central stage. Silicone represents one of the most prevalent adjuvants to be associated with ASIA syndrome (autoimmune/inflammatory syndrome induced by adjuvants), encompassing a spectrum of immune mediated diseases (2). There are few case reports describing MPO+ ANCA vasculitis occurring after silicone breast implantation with only one case (3) describing a development of MPO-positive GPA manifesting 28 years after silicone implant surgery. Our case is the first to report the development of GPA with PR3+ ANCA antibodies in a patient with 3 years history of silicone breast implants. In our case, symptoms of GPA were initially, for 8 weeks mainly localized to implanted breast tissue along with constitutional symptoms, primarily suggesting silicone-induced autoimmune reaction. Gradually, a full-blown GPA developed. Additionally, a recent vaccination in our patient could exacerbate the underlying adverse immune reaction. Vaccines are well known triggers for development of ASIA syndrome, confirmed by recent reports of auto-immune phenomena after COVID-19 vaccinations (4-6). This indicates that rarely, vaccination might activate immune system to react towards implanted materials, such as silicone. Our patient developed first symptoms five weeks after the second vaccine dose, making a temporal association of GPA with only vaccination questionable. Instead, we speculate a two-hit model: silicone implants presumably induced chronic adverse reaction of immune system that was acutely exacerbated by vaccine-trigged immune activation, culminating in a severe GPA.

In conclusion, our case shows that ASIA syndrome may manifests as anti-PR3+ granulomatosis with polyangiitis. Thus, silicone breasts implants should be considered as an environmental trigger of ANCA vasculitis.

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