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Title:

Liver Graft Outcomes from Donors with Vaccine Induced Thrombosis and Thrombocytopenia (VITT): United Kingdom Multi-Centre Experience

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ABBREVIATIONS:

HAT: Hepatic artery thrombosis

HIT: Heparin induced thrombocytopenia

LT: Liver transplantation

PF4: Platelet factor 4

TMAT: Transplantation mediated alloimmune thrombocytopenia

UK: United Kingdom

VITT: Vaccine induced immune thrombocytopenia and thrombosis

Dear Editor,

Vaccine-induced immune thrombosis and thrombocytopenia (VITT) syndrome is a new entity, characterised by severe thrombocytopenia and multiple sites of thrombosis[1]. The presumed mechanism is driven by anti-platelet factor 4 (PF4) antibodies causing platelet activation[1]. Donors with VITT syndrome have a particular relevance for liver transplantation (LT), due to the associated risk of passenger lymphocyte syndrome, and a predisposition for porto-mesenteric or hepatic vein thrombosis all[2]. The early United Kingdom (UK) experience on pan-solid organ transplants from VITT donors has been briefly documented and sent a cautionary message to the transplant community[3], meanwhile the recent French series only included one liver transplant recipient[4]. Our aim is to describe longitudinal outcomes of liver grafts transplanted in the UK from donors with VITT syndrome thus far, so that both clinicians and patient can more accurately consider the risk-benefit equation under the caveat emptor principle ("buyer beware") when utilising these organs, as suggested by Wolfe et al[5].

Prior to the initial description of VITT syndrome in early April 2021, seven LT were from donors with VITT syndrome, plus two further LT performed following the review of early outcomes, and appropriate risk-benefit assessments. All donors (n=8, aged between 22-55years) had catastrophic intracerebral haemorrhage or thrombosis, and had received the first dose of ChAdOx1 nCOV-19 vaccine 9 to 19 days before hospital admission. One liver was split into an extended right lobe and left lateral segment. Recipients' (n=9, aged 2-43years) indications for LT included hepatoblastoma(1), seronegative hepatitis(1), late hepatic artery thrombosis(HAT, 2), primary sclerosing cholangitis (PSC,2), recurrent PSC(1), Budd-Chiari syndrome(1) and alcohol-related liver disease(1). Therapeutic anti-coagulation post-transplantation was empirically started in three recipients with Budd Chiari syndrome and late HAT. PF4 IgG-antibodies were assessed by enzyme linked immunosorbent assay and four recipients had positive (>0.40 optical density) levels early in the postoperative period (day 2-

18). None of these recipients had bleeding or thrombotic complications; two were commenced on therapeutic anticoagulation [Apixaban or fondaparinux]. One recipient was anticoagulated with argatroban and then danaparoid based on the donor diagnosis of VITT, and experienced intra-abdominal and gastrointestinal bleeding early post-transplant. Severe thrombotic events occurred in the two recipients of the split liver grafts derived from the same donor, requiring emergency re-transplantation within the first 7 postoperative days, but no anti-PF4 antibodies were detected. Histologic finding suggested vascular thrombosis was likely pre-existing in the donor (Figure 1). So far, all recipients in the UK have more than 3 months follow-up, and are alive at the time of writing with good liver functions, including two recipients that underwent re-transplantation.

Since this entity emerged, 19 brain-dead donors with VITT syndrome in the UK have had organs offered for transplantation, only the 9 liver grafts (from 8 donors) presented in this manuscript were transplanted. This signifies scepticism within the transplant community. Our current understanding, based on limited experience, is that safe transplantation of livers from these donors is still possible, with the main concern being pre-existing vascular thrombosis in the graft[2]. With the continued global administration of the ChAdOx1 nCOV-19 vaccine, donors with VITT syndrome are likely to continue and should be given the appropriate consideration for transplantation.

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CONFLICTS OF INTEREST

Authors:

Angus Hann has no conflicts of interest to disclose as per *the American Journal of Transplant*

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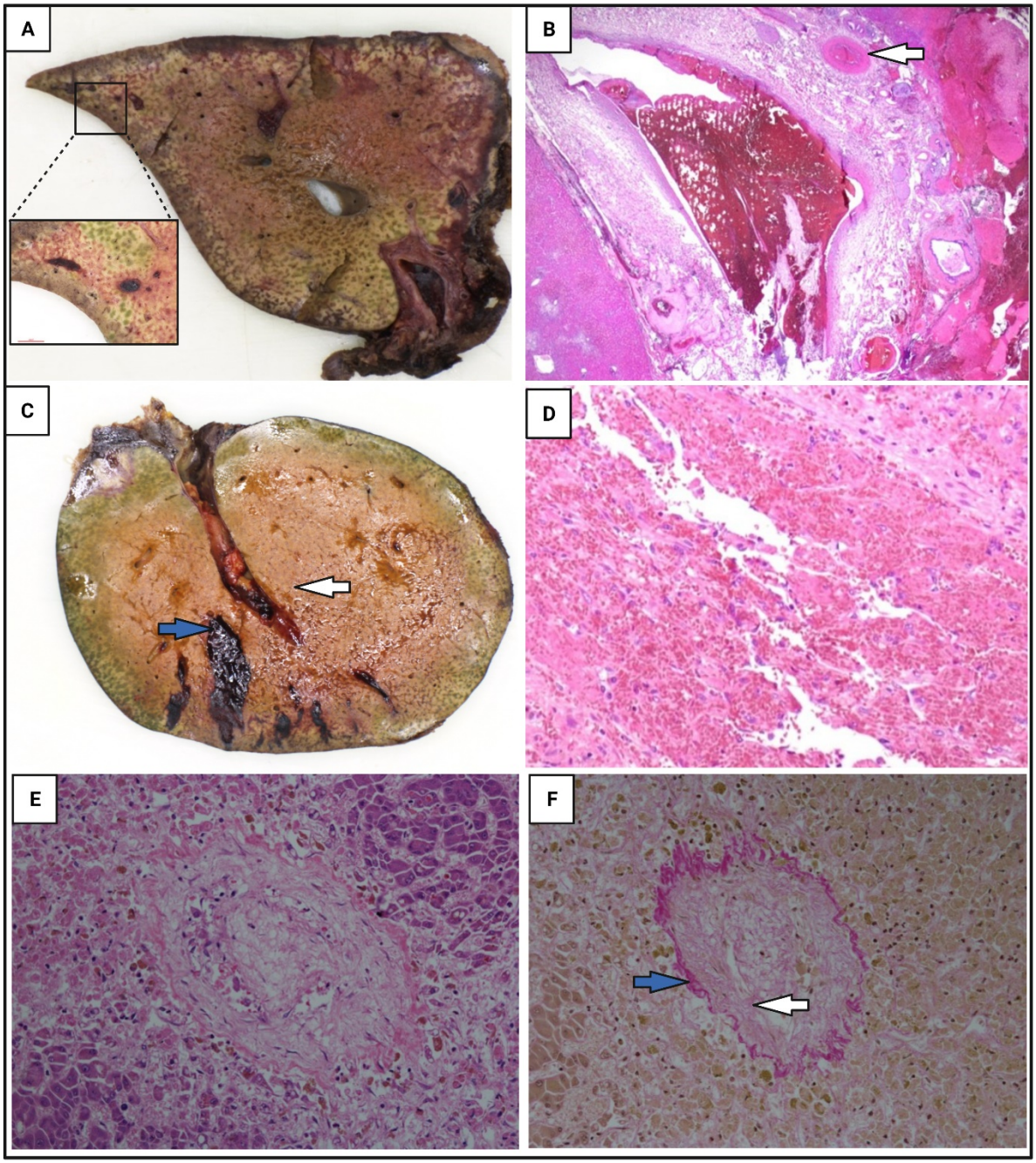
FIGURE 1



LEGEND: Images demonstrating failed grafts; Left lateral segment (A&B), Extended right lobe (C-F). A) Slice of explanted left lateral segment with clot evident in portal vein (lower right). Inset demonstrates thrombus within peripheral hepatic vein branches. B) Histology image (Haemotoxylin and Eosin stain) of explanted left lateral segment showing thrombus in portal vein and hepatic artery (arrow). C) White thrombus evident macroscopically in the hepatic vein (White arrow) and fresh thrombus in intrahepatic portal vein (Blue arrow). D) Haematoxylin and eosin stain of explanted liver showed organising thrombus with granulation tissue, suggesting it may have occurred within the donor. E & F - Haematoxylin and Eosin stain (E) and haematoxylin and Van Gieson (F) stain demonstrating thrombosed hepatic vein with early collagen (pale pink, white arrow) deposition around the thrombus. This suggests thrombosis had been organised and may have occurred prior to

transplant, rather than in the 4 post-operative days. The mature collagen within the vessel wall (dark pink) is marked with a blue arrow.