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CASE REPORTS / CASE SERIES

Perioperative management of an IgA-deficient recipient of a double-lung transplant

Gestion périopératoire d'un patient receveur d'une double transplantation pulmonaire et ayant un déficit en IgA

Asim Alam, MD · Christine M. Cserti-Gazdewich, MD

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Abstract

Purpose *When exposed in the perioperative period to blood components containing immunoglobulin (Ig)A IgA-sensitized IgA-deficient patients are at an increased risk of transfusion-associated anaphylaxis. We present the case of an IgA-deficient patient whose candidacy for double-lung transplantation was under review in the preoperative period.*

Clinical features *A 49-yr-old patient with end-stage chronic obstructive lung disease secondary to deficiencies in IgA and IgG subclasses was being assessed for double-lung transplantation. Early recognition of the ramifications of perioperative transfusion prompted consultation with the transfusion medicine service. This in turn facilitated specialized laboratory testing and the coordinated provision of appropriate blood products for the unpredictable date of transplantation. The theoretical systemic risks of a non-IgA-deficient graft on the sensitized IgA-deficient host were considered. To affirm the patient's candidacy for transplantation, he was ultimately challenged preoperatively with IgA-containing products in a controlled intensive-care setting.*

Conclusion *Through a multidisciplinary, a successful transplantation outcome was achieved in an IgA-deficient patient undergoing major surgery. Strategies to mitigate risk include the procurement and transfusion of IgA-deficient components, which may be challenging or untenable in emergent perioperative settings.*

Résumé

Objectif *Les patients ayant un déficit en immunoglobulines (Ig) A sensibilisés aux IgA ont un risque augmenté d'anaphylaxie associée aux transfusions quand ils sont exposés à des produits sanguins contenant des IgA. Nous présentons le cas d'un patient ayant en déficit en IgA dont la candidature à une double transplantation pulmonaire était examinée en période préopératoire.*

Caractéristiques cliniques *Un patient âgé de 49 ans atteint de maladie pulmonaire obstructive chronique au stade terminal secondaire à des déficits en sous-classes d'IgA et d'IgG faisait l'objet d'une évaluation en vue d'une double transplantation pulmonaire. L'identification précoce des ramifications des transfusions périopératoires a entraîné une collaboration avec le service de médecine transfusionnelle. Cela a débouché sur des tests de laboratoire spécialisés et un approvisionnement coordonné en produits sanguins adaptés pour la date imprévisible de la transplantation. Les risques systémiques théoriques d'une greffe non*

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A. Alam, MD (✉)
Department of Anesthesia, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, ON M4N 3M5, Canada

A. Alam, MD · C. M. Cserti-Gazdewich, MD
Department of Laboratory Medicine & Pathobiology, University of Toronto, Toronto, ON, Canada

C. M. Cserti-Gazdewich, MD
Division of Hematology, Department of Medicine, University of Toronto, Toronto, ON, Canada

C. M. Cserti-Gazdewich, MD
Transfusion Medicine, University Health Network, Toronto, ON, Canada

déficitaire en IgA sur un hôte sensibilisé ayant un déficit en IgA ont été abordés. Pour confirmer la candidature définitive du patient à la transplantation, il a finalement été exposé en préopératoire à des produits contenant des IgA dans un cadre contrôlé de soins intensifs.

Conclusion *La transplantation a été réussie grâce à une approche multidisciplinaire chez un patient présentant un déficit en IgA et devant subir une intervention chirurgicale majeure. Les stratégies visant à réduire le risque incluent l'approvisionnement et la transfusion de produits dénués d'IgA, ce qui peut être très difficile, voire impossible à réaliser dans un contexte périopératoire inattendu.*

Since their description in 1968, immunoglobulin (Ig)A antibodies have dominated as the serologic marker of severe anaphylactic transfusion reactions towards IgA-containing blood products.[1,2] International registries of IgA-deficient donors have been established to provide IgA-deficient blood products to IgA-deficient recipients who have IgA antibodies, thereby preventing confrontation of IgA altogether.[1] Transfusion medicine specialists typically recommend that transfusion-associated anaphylaxis cases be screened for IgA deficiency and antibodies, with indefinite restriction to IgA-deficient/depleted blood products if verified.[1,2] The extent to which the implications of IgA deficiency are recognized amongst surgeons and anesthesiologists is unclear.

Lung transplant recipients often require blood components perioperatively, thereby encountering significant quantities of IgA. When IgA-sensitized IgA-deficient patients are considered for lung transplantation, the hospital transfusion service is faced with the challenge of preparing an adequate supply of safe components on short and imprecise notice in a timely fashion. The opportunity to prepare is further curtailed when a transplant recipient has not been reviewed by the transfusion medicine service in advance of graft procurement. There are no established guidelines, let alone case reports, for the management of incipient lung transplantation in those with IgA deficiency and possible or definite anti-IgA antibodies. We report on the preoperative assessment of an IgA-deficient lung transplant candidate for perioperative considerations and contingencies for transfusion care. The patient provided written consent for publication of this case.

Case presentation

A 49-yr-old patient with end-stage chronic obstructive lung disease secondary to deficiencies in IgA and IgG subclasses was referred to the pre-anesthetic consult clinic in advance of double-lung transplantation. He was a former smoker and carpenter exposed to occupational dusts with an uneventful history of minor surgical procedures. Medications consisted of inhalers, a proton-pump inhibitor, and chronic antibiotic therapy. Over the previous year, he was also receiving intravenous immune globulin (IVIG) (Privigen, CSL Behring) for humoral immune reconstitution and was experiencing only mild reactions (headaches). He had no other blood transfusion history.

At clinic, his pulmonary function indices were indicative of end-stage lung disease. The echocardiogram was normal. His complete blood count showed hemoglobin 135 $g{\cdot}L^{-1}$, mean corpuscular volume (MCV) 95.1 fL, and platelet count 544 $\times$ 10^9 L^{-1}. The coagulation profile was within normal limits. Room air arterial blood gas measured pH 7.42, P_aCO_2 46 mmHg, P_aO_2 62 mmHg, and bicarbonate 30 mM. His blood type was AB, Rh(D)-positive, with a negative red cell antibody screen.

The transfusion medicine service was consulted to confirm and classify the diagnosis for the most appropriate blood management. Reference laboratory testing (American Red Cross, Penn-Jersey IRL, PA, USA) was undertaken for the precise quantitation of IgA (by sensitive enzyme-linked immunosorbent assay) and for the detection of anti-IgA IgG (by passive hemagglutination). Immunoglobulin A was indeed detected at a low level (0.05-6.0 $mg{\cdot}dL^{-1}$), but results on anti-IgA would not be available within the preferred timeframe of transplantation.

During the interim period of uncertainty, the precautionary approach was therefore adopted with the aim to prepare products suitable for an IgA-deficient (potentially sensitized or post-exposure sensitizing) recipient. We made arrangements with both our hospital and collector/provider (Canadian Blood Services) for an appropriate quantity of red blood cell units to be washed and available. Due to the confirmed paucity of IgA-deficient group AB plasma units in the national inventory, additional collections of plasma units were requested. The acquisition of IgA-deficient platelet products posed the greatest challenge; their short shelf life (five days at room temperature) and the limited number of IgA-deficient donors rendered extremely low odds of incidental and proximal availability within a six-hour window for pre-transplant notification. In the situation of non-availability, the time from donor summons to collection and release was expected to provide a concentrate no sooner than postoperative day 2-3. The patient's fortuitous (benign) thrombocytosis was regarded as being theoretically conducive to preoperative platelet apheresis self-donation, therein serving to bridge any incidental gaps in access to platelets for up to five days. Each of the above tactics would secure an adequate stock of products to support transfusion during the transplantation.

The ongoing uncertainty in the patient's capacity to handle IgA was thought to represent the most serious ethical challenge to listing him for transplantation. Indirect evidence against the existence of anti-IgA antibodies was mounting due to detectable (trace) levels of IgA and ongoing tolerance of IVIG. Thus, the necessity for IgA-deficient products and the danger of exceeding the finite appointed supply thereof were still unknown. A controlled administration was proposed in order to be better informed of the risks of crossing over to unmodified products and to acknowledge the possibility that the graft itself might be a source of (perhaps even more substantial) IgA exposure. The patient consented to an elective *in vivo* challenge with dose-control and anaphylaxis support and was thereby dissociated from potential threats to (or from) a potential lung allograft. A single unit of plasma was therefore scheduled for administration in the intensive care unit with acceptance of the risks of immediate allergenicity or an abundance-triggered primary IgA seroconversion prior to transplantation. A 250-mL unit of plasma was infused in increasing volumes (starting at < 1 mL·min^{-1}) over a two-hour period. The patient remained hemodynamically stable with no signs of acute or delayed anaphylaxis from an anamnestic response. The event-free exercise ultimately qualified him for both transplantation and unmodified blood products.

Canadian Blood Services adopted a "research use only" assay for anti-IgA IgG detection (ID-PaGIA anti-IgA test, DiaMed, GmbH, Cressier, Switzerland),[3] which was also offered to the patient in this period between consultation and transplantation. A negative result two months later was taken as further reassurance.

Four months after transfusion medicine consultation, the patient underwent a double-lung transplant with no requirement for blood products. He was resuscitated with crystalloid 2,500 mL and 6% hydroxyethyl starch (Voluven, Fresenius Kabi) 500 mL. The estimated blood loss was 200-500 mL. He was transferred to the intensive care unit (ICU) postoperatively and discharged home on postoperative day 17 with minimal complications. To date, he has not been re-exposed to blood components.

Discussion

We report a case of double-lung-transplantation in an IgA-deficient patient and describe the complexities and uncertainties of organizing the safest possible transfusion support. This case illustrates the daunting logistics applicable to IgA-deficient patients in the perioperative planning process, especially when the precise timing and maximal transfusion needs of the procedure are largely unpredictable. Risk management anticipates the hazards of transfusion with transplantation as well as the requisite mitigation strategies. These are then weighed against the consequences of altogether denying the patient a life-saving transplant while determining special exceptions. Indeed, a history of IgA deficiency with anti-IgA is not an absolute contraindication to surgical procedures requiring large-volume transfusion support, even if severe anaphylactic reactions to blood transfusions have occurred.[4,5] The onus is therefore on the perioperative transplant physicians to make a reasonable estimate of the IgA-deficient patient's risk of anaphylaxis and to involve the blood collector and hospital transfusion service in amassing the most suitable transfusion resources. Fortunately, this patient neither developed anaphylaxis on a preoperative IgA challenge nor required substantial blood component products. Consequently, the bulk of precautions and actions were not required.

The prevalence of IgA deficiency is not uncommon, with approximately one in 2,000 individuals affected; however, symptoms appear in only one in 500-700 of these individuals.[6] The IgA-deficient patient's plasmacytes are unable to produce IgA, although B-lymphocyte quantity is normal. Major IgA deficiency is associated with repetitive sinopulmonary infections, otitis, meningitis, and pneumonia.[6] These patients may also have asthma, allergies, and gastrointestinal to urinary tract infections. IgA-deficient patients are also at risk of autoimmune diseases such as immune thrombocytopenia, rheumatoid arthritis, and lupus erythematosus.[6] Perioperative case review should therefore also screen by history and physical exam for these conditions and aim for their optimization before elective procedures.

Normal serum titers of IgA range from 100-400 mg·dL^{-1}, while levels in patients with selective IgA immunodeficiency are often < 7 mg·dL^{-1}.[6] The diagnosis of IgA deficiency is established by IgA serum levels of < 0.05 g·dL on at least two occasions, with undetectable secretory IgA and the absence of other primary and secondary immunodeficiencies.[6] The management of symptomatic IgA deficiency is dedicated to the prevention of infections and the administration of appropriate antibiotics when they do occur.[6]

IgA-deficient (or variant) individuals who sensitize to IgA are believed to therein have heightened odds of anaphylactic shock when IgA-containing blood products are given.[6] Nevertheless, in a large study of anaphylactic transfusion reactions, anti-IgA was detected in only 18% of the cohort, and conversely, anti-IgA was detected in one in 1,200 random blood donors.[7] Not all patients with anti-IgA have anaphylactic transfusion reactions, and only the minority of anaphylactic transfusion reactions are caused by anti-IgA. Nevertheless, the prevailing understanding is that sensitized IgA-deficient patients constitute those at a particularly high risk of transfusional anaphylaxis.[4]

Ascertaining anti-IgA antibodies in IgA-deficient patients is strongly recommended prior to major surgeries, as the precautionary consensus is to avoid IgA-containing products.[2] Nevertheless, cellular products need not necessarily derive from IgA-deficient donors. Immunoglobulin A-deficient red blood cells can be achieved by washing with 0.9% saline. When cycled three times, nearly 99% of the IgA content is removed, although standard washers shorten the processed component's shelf life to 24 hr.[2] Platelet products may be washed and re-suspended in crystalloid solutions, although washing activates a certain proportion of platelets and may diminish product function.[8] Preoperative autologous blood donation may be considered if collection technologies are available and time permits.[4]

Although IgA-deficient blood components are considered the "gold standard" in safety,[4] in emergent situations, such as deceased donor transplantation, it may be impossible to procure the desired product repertoire. Prophylactic steroids may be considered when non-IgA-deficient components are transfused, although evidence for this is lacking.[4] Recent work has focused on the prevention of IgA anaphylaxis by pretreatment tolerance-induction techniques using blood products with low IgA content, such as IVIG.[9,10] In our case, a year-long pretreatment with IVIG may have inadvertently served as a desensitizing tolerance induction therapy, as the patient had no reaction on exposure to the plasma challenge in the ICU. Conversely, the IVIG may have been the passive source of detectable IgA, therein falsely implying partial deficiency and raising hazardous expectations of tolerance at the time of experimental plasma infusion.

The emphasis on amassing IgA-deficient blood products ignores the consideration of the graft itself as a potentially more substantial secretory source of IgA within the intended recipient. Systemic translocation of IgA on anastomosis might provoke anaphylaxis despite meticulously prepared blood products and suggest failures in the quality of the latter. Alternatively, the systemic influx may be delayed or occur in the setting of a transfusion-free procedure. The onset of a prolonged pressor-dependent postoperative hypotension with distributive shock and/or severe allergic bronchospasm may be misdiagnosed or misattributed to other exposures.

Nonetheless, the peril of graft-sourced IgA may prove to be self-limited by a number of mechanisms. First, passenger lymphocytes in the graft may be eradicated by host immunity within weeks to months.[11] Second, active IgA secretion might not occur, and passive IgA may be the only menace with a much sooner clearance on the basis of a half-life of only six days. Third, the IgA may be secreted so persistently and copiously so as to induce tolerance by the host, thereby also potentially curing the underlying deficiency. The hope of the latter is challenged however by the high prevalence (up to 73%) of hypogammaglobulinemia observed after lung-transplantation.[12] Ultimately, the presence of IgA in the graft has previously been considered a minimal and worthwhile risk in such patients.[4]

In summary, the theoretical considerations applicable to an IgA-deficient candidate for lung transplant are challenging precisely because guidelines are lacking. For better or worse, seeking certainty on the matter of tolerance prompted the precarious trial of plasma. The consenting patient earned a less insecure transplantation experience by virtue of his well-demonstrated tolerance to this substantial IgA exposure. It remains to be determined whether his outcome is generalizable amongst future patients in a similar position. Nevertheless if he had suffered anaphylaxis, we would have "ruled in" the odds of the same (or worse) occurring on IgA re-exposure and would then have the currency of an indisputable event by which to commit to (and demand) greater volumes of IgA-depleted products. The informed consent process regarding the transplantation procedure would also thus be strengthened for every party, be it the patient, those governing the scarce resource of lung transplants, and the transplantation team itself.

In our view, interprofessional collaboration between transfusion medicine specialists, surgeons, and anesthesiologists was a cornerstone in the successful management of this patient. The daunting call to provide unpredictable volumes of safe products at unpredictable times for IgA-deficient patients demands a synergy of care and contingency planning.

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