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Case Report

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IGG2 Subclass Deficiency: A Potential Risk Factor of Recurrent Severe Infection to Be Suspected After Complex Surgery

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Abstract

IgG2 subclass deficiency is the most common type of IgG subclass deficiency. Immunological monitoring of components of humoral immunity such as IgG subclasses is not included in the evaluation protocols for hospitalized patients who develop serious infections after complex surgery. We report on a patient with IgG2 subclass deficiency who developed severe recurrent bacterial and viral infections after complicated thoracic surgery.

Keywords: *Immune monitoring, IgG2 subclass, Infection, Heart surgery.*

Introduction

IgG2 subclass deficiency is the most common type of IgG subclass deficiency. Patients with this primary antibody deficiency usually suffer from frequent upper and lower respiratory tract infections. In some cases, they may develop autoimmune complications. Immunological monitoring of components of humoral immunity such as IgG subclasses is not included in the evaluation protocols for hospitalized patients who develop serious infections after complex surgery. Some centers perform immunoglobulin determinations in these cases, but IgG subclass defects present with normal levels of total IgG. We report on a patient with IgG2 subclass deficiency who developed severe recurrent infections after complicated thoracic surgery.

Presentation of the case

The patient was a 66-year-old white woman with a personal history of hypothyroidism following left hemithyroidectomy for a thyroid nodule. She had cardiac tamponade due to advanced intracardiac angiosarcoma of the right atrium, with multiple supradiaphragmatic lymph nodes and bone involvement. Cardiac magnetic resonance imaging revealed a partial response to chemotherapy. She was admitted in October 2022 for scheduled surgical resection, which was performed successfully. Resection of the right atrium, tricuspid valve, and proximal portion of the right ventricle was performed with implantation of a St. Jude Epic No. 31 biological prosthesis. Reconstruction was based on a heterologous pericardial patch combined with myocardial revascularization with a graft from the saphenous vein to the distal right coronary artery. The procedure was without incident.

The patient was transferred to the post-surgical intensive care unit (ICU), but had to undergo further surgery owing to excessive bleeding. Hemostasis was restored, and she was taken back to the ICU.

During admission, the patient developed hypoxemic respiratory failure due to *Aspergillus* infection, which required prolonged respiratory assistance, reintubation, and tracheostomy for respiratory weaning. Culture revealed growth of *Pseudomonas mosselii* and *Citrobacter freundii*, as well as reactivation of severe herpes zoster infection with extensive involvement. These findings co-occurred with pulmonary herpes simplex infection. Cytomegalovirus (CMV) infection was detected using polymerase chain reaction (PCR) assay. The patient also had acute kidney failure requiring ultrafiltration in the context of cardiogenic shock, which required prolonged vasoactive support. Transthoracic and transesophageal echocardiograms revealed mitral regurgitation requiring placement of a MitraClip, which resulted in moderate residual regurgitation.

Given the severity of the herpes zoster infection, ICU consulted with the clinical immunology department to evaluate the patient's immunocompetence in more detail. Further examination of her clinical history revealed bacterial pneumonia, recurrent respiratory infections, and vaccination against pneumococci, tetanus-diphtheria, hepatitis B, influenza, and COVID-19 (3 doses).

Exploration, complementary tests and interventions included repeated fiberoptic bronchoscopy, pleural drains, tracheotomy, and MitraClip. Chest computed tomography (CT) disclosed bilateral pulmonary consolidations and

opacities suggestive of an infectious process. Follow-up imaging showed partial improvement of the bilateral pulmonary consolidations. CT of the abdomen and pelvis with IV contrast showed sigmoid diverticulosis and free fluid in the pelvis and flanks. Histopathology of a lung biopsy specimen revealed fungi with septate hyphae, branching occasionally at 45º and initially suggestive of *Aspergillus*. Cytology of a biopsy specimen from the neck demonstrated a cytopathic effect attributable to herpesvirus infection. Analysis of a cardiac sample based on partial resection of the heart (right atrium, tricuspid valve, and proximal portion of the right ventricle) after chemotherapy revealed cardiac angiosarcoma (maximum diameter, 3.7 cm), high grade (epithelioid and spindle cell morphology). Immunohistochemistry revealed ERG+, CD31+, CD34–, with areas of necrosis and perineural infiltration.

The microbiology results were as follows:
2022.10.29. Urinary extended-spectrum beta lactamase–producing *Escherichia coli*.
2022.11.03. *Trichosporum mucoides*, *Candida sp*.
2022.11.04. *Aspergillus sp*, galactomannan-negative.
2022.11.07. *Trichosporum mucoides*, *Candida albicans* and *glabrata*, and *Aspergillus sp.*
2022.11.11. Bronchial alveolar lavage disclosing positive PCR for herpes simplex virus.
2022.12.01. PCR positive for CMV in blood.
2022.12.02. Blood culture, bronchial aspirate, urine, and rectal exudate: *Citrobacter freundii* (sensitive to ciprofloxacin and meropenem). Blood culture revealed *Pseudomonas mosselii*.

An extended immunological evaluation performed on 2022.11.18 was remarkable for total lymphopenia (700 cells/µL [normal value, 1200-4000 cells/µL]) and revealed low levels of CD3 (455 [743-2250 cells/µL]), CD4 (350 [380-500 cells/µL]), CD8 (15% [28-38%]), and CD19+ (B cells, 13% [20-40%]). NK levels (CD3-CD16+/CD56+) were normal (12% [4-28%]). The neutrophil count was normal (5800 [1500-7500 cells/µL]), as was the monocyte count (200 [200-1000 cells/µL]). Evaluation of humoral immunity on 2022.11.23 disclosed low levels of IgG2 (229 [242-700 mg/dL]). Other IgG subclasses were within the normal range, as follows: IgG1, 684 (382-929 mg/dL); IgG3, 87.5 (22-176 mg/dL); and IgG4, 33.7 (4-86 mg/dL]. Retesting of IgG2 subclass confirmed low levels for IgG2 (181.5 [242-700 mg/dL]). Normal values were recorded for total IgG (876 [700-1600 mg/dL]), IgA (92 [70-400 mg/dL]), and IgM (55 [40-230 mg/dL]. Complement C3 and C4 were within normal values. C-reactive protein levels were high (89.9 [0.1-10 mg/L]).

In the post-surgical ICU, the patient developed recurrent mixed nosocomial and opportunistic infections (extensive severe herpes zoster infection, invasive pulmonary aspergillosis, nosocomial pneumonia associated with mechanical ventilation, bacteremia secondary to respiratory infection, and urinary tract infection) associated with the health care required for her critical situation.

Given the severe herpesvirus infection, compassionate use therapy was associated with anti-CMV intravenous immunoglobulin (5% CMV-IVIG, preparation with a higher concentration of CMV and EBV virus antibodies than non-specific conventional preparations). A protocol of 100 mL per week was used until herpes zoster was controlled.

As indicated above, the patient had several bacterial infections, and IgG2 subclass deficiency was confirmed twice. Therefore, once herpes zoster infection was controlled, we recommended switching from CMV-IVIG to non-specific IVIG at a dose of 20 grams IV every 30 days using a slow IVIG infusion protocol. The infusions were administered without complications. We observed gradual control of infection during this admission after IVIG was added. T- and B-cell lymphopenia may have also contributed to the patient's recurrent infections.

During follow-up, the patient was discharged to the general ward on the 74th postoperative day. Given the good progression of the infectious, cardiac, and respiratory symptoms, she was discharged on the 86th postoperative day. IVIG infusions of 20 grams every 30 days were prescribed after discharge. The patient subsequently attended the day hospital for therapy with IVIG according to the indicated regimen. There has been no recurrence of severe infection, and the patient's quality of life was good for 3 months after discharge, when progression of the angiosarcoma was observed. The disease progressed to multiple bones, with L1 and L5 spinal cord compression and risk of canal invasion at C6 and T4. Pulmonary, hepatic, splenic, pericardial, and possible pleural progression were also demonstrated. The patient developed mild COVID-19. She eventually died from complications of metastatic angiosarcoma.

Discussion

The isolated IgG2 defect was striking at the time cumulative evidence of severe infections was demonstrated after complex surgery for angiosarcoma. Therefore, the presence of a baseline primary IgG2 subclass deficiency cannot be ruled out [1]. Patients with isolated IgG2 deficiency usually require medical attention for recurrent symptoms of sinusitis, otitis media, and pulmonary infections, as seen through the previous history of the patient reported here. Affected persons may experience chronic inflammation with pulmonary fibrosis or bronchiectasis. Given the recurrent infections and IgG2 subclass deficiency detected in the present case, replacement treatment with IVIG was indicated.

IgG2 subclass deficiency may also be secondary and correlate with the development of the same events that the patient presented, although it is usually associated with a more extensive profile of humoral immunodeficiencies that the patient did not have [2, 3]. IgG subclass deficiency has been significantly associated with shorter treatment-free survival and disease severity in patients with chronic lymphocytic leukemia [4].

Conclusion

Therefore, we conclude that the recurrence and severity of infections in this patient were due, at least in part, to IgG2 deficiency. Management of severe recurrent or mixed infections in the ICU should include screening for immunodeficiency.

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