Could multisystem inflammatory syndrome in adults after COVID-19 have different presentations in kidney transplant recipients - a report of two cases

Armin Atic[1], Ivana Juric[1], Lea Katalinic[1], Vesna Furic-Cunko[1], Ana Strizic[2], Jasmina Matijasevic Skerlj[3], Zoran Sabljic[1], Nikolina Basic-Jukic[1]

[1] University Hospital Center Zagreb, Department of Nephrology, Dialysis, Arterial Hypertension and Transplantation, Kispaticeva 12, Zagreb, Croatia
[2] Clinical Hospital Dubrava, Department of Nephrology, Av. Gojka Suska 6, Zagreb, Croatia
[3] University Hospital Center Zagreb, Clinical Pharmacy, Kispaticeva 12, Zagreb, Croatia

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Correspondence:
Armin Atic
armin.atic@kbc-zagreb.hr

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Abstract:

Multisystem inflammatory syndrome after COVID-19 (MIS-A) is a consequence of an abnormal inflammatory response after COVID-19 resolution. Current criteria for diagnosis consist of the involvement of several organ systems. We present two cases, one in an immunosuppressed kidney transplant recipient and one in a patient on hemodialysis currently not on immunosuppression. The different clinical presentations and disease development may indicate that the current criteria for MIS-A diagnosis may be inadequate for immunosuppressed patients, as chronic immunosuppression may alter disease presentation. Both patients were treated with corticosteroids and intravenous immunoglobulins, and in both cases the treatment resulted in a prompt resolution of symptoms and stabilization of inflammatory parameters.

Keywords:

MIS-A; kidney transplantation; intravenous immunoglobulin, COVID-19

Sažetak:

Može li multisistemski upalni sindrom kod odraslih nakon COVID-19 imati različite prezentacije kod primatelja presađenog bubrega – prikaz dva slučaja

Multisistemski upalni sindrom nakon COVID-19 (MIS-A) je posljedica pretjeranog imunosnog odgovora nakon preboljenja akutnog COVID-19. Trenutno važeći kriteriji za dijagnozu zahtijevaju zahvaćanje više organskih sustava. U ovom radu prikazana su dva slučaja, jedan u imunosuprimiranog bolesnika s presađenim bubregom i jedan u bolesnika na kroničnoj hemodijalizi bez imunosupresivne terapije. Različite kliničke prezentacije i tijek bolesti ukazuju na moguću neadekvatnost kriterija za postavljanje dijagnoze MIS-A u imunosuprimiranih bolesnika. Kod njih je moguće da kronično imunosuprimirano stanje mijenja prezentaciju bolesti. Oba bolesnika liječena su kortikosteroidima i intravenskim imunoglobulinima. U oba slučaja došlo je do brzog razrješenja simptoma i normalizacije upalnih parametara.

Ključne riječi:

MIS-A; transplantacija bubrega; intravenski imunoglobulin, COVID-19

Introduction

Multisystem inflammatory syndrome following COVID-19 was initially described in children, however, it was soon recognized in adults. It is characterized by the onset of new symptoms following the resolution of acute COVID-19, most typically fever, skin rash, cardiac dysfunction, diarrhea and shortness of breath[1, 2]. In comparison to children, multisystem inflammatory syndrome in adults (MIS-A) more frequently presents with signs of myocarditis, cardiac dysfunction and arterial or venous thrombosis[1]. MIS-A following COVID-19 is thought to be MIS-A triggered by a dysfunctional immune response leading to systemic inflammation, endothelial dysfunction and a procoagulant state. The US Center for Disease Control and Prevention (CDC) has issued clinical criteria for the definition of MIS-A and these include fever and primary criteria of cardiac involvement and/or skin rash and secondary criteria including new onset neurological symptoms, hypotension not attributable to medical therapy, abdominal symptoms including diarrhea and thrombocytopenia. Laboratory evidence must include elevated levels of at least two of the following: C-reactive protein (CRP), ferritin, IL-6, erythrocyte sedimentation rate, procalcitonin and a positive SARS-CoV-2 test for current or recent infection by RT-PCR, serology, or antigen detection[3]. For diagnosis, one of the criteria must be met by the third day of hospital admission. MIS-A has not been reported in kidney transplant recipients. In this paper we present a report of two cases with similar initial presentations successfully treated with intravenous immunoglobulins.

Case 1

A 41 year-old male presented to the emergency department with dyspnea, chest pain and fever. Initial work-up revealed mildly elevated inflammatory parameters (CRP 26,5 mg/L) and a hemodynamically insignificant pericardial effusion. His medical history was extensive and involved chronic kidney disease since childhood (membranoproliferative glomerulonephritis type I), treated with hemodialysis for seven months until kidney transplantation from a related donor in 2007. In 2013 he developed proteinuria due to a biopsy-proven relapse of MPGN which required treatment with rituximab three years later. In 2019, due to terminal graft failure the patient was reevaluated for a second kidney biopsy and was started on chronic hemodialysis. In January 2023 a graftectomy was performed due to recurring hematuria. His other comorbidities included severe malnutrition and protein-energy wasting, anaemia of chronic disease, arterial hypertension and secondary hyperparathyroidism. He was on chronic hemodialysis 3x weekly, and his chronic medication list included moxonidine, lercanidipine, carvedilol, pantoprazol, urapidil, sevelamer carbonate, paricalcitol, erythropoietin beta and iron supplementation on dialysis days and enteral supplementation drinks. Prior to admission, the patient had COVID-19 on three occasions, the last one two months prior to presentation and was vaccinated for SARS-CoV-2 four times. The patient was admitted and standard treatment for pericarditis with indomethacin and colchicine was initiated. Due to persisting fevers, five days later the patient was transferred to the department for transplanted patients. The differential diagnosis included tuberculosis, atypical infections or a lymphoma of the pericardium, and an extensive work-up including a CT, bronchoscopy, PET scan, and a barrage of bacteriological, virological, mycological, mycobacterial and immunological tests was performed. On admission, wide-spectrum antibiotics were initiated (piperacillin/tazobactam). Despite the therapy, the fevers persisted and inflammatory markers were rising (CRP increase to 268.1 mg/L, PCT 2,46 ug/L), with worsening dyspnea due to a progressing pericardial effusion, however, the patient was hemodynamically stable. The effusion was unavailable for pericardiocentesis. A CT scan of the chest, abdomen and pelvis revealed a diffuse lymphadenopathy. Antibiotic regimens were changed on several occasions, and the overall treatment included vancomycin, meropenem, ceftazidime/avibactam, metronidazole and others. Fevers still relapsed 3x weekly with no following symptoms, and the inflammatory markers remained high (C-reactive protein (CRP 180.4-255.4 mg/L, PCT 1.8-2.46 ug/L). Four weeks after admission, the patient developed a new pattern of persisting fever with a further increase of inflammatory markers, and a PCR for SARS-CoV-2 came positive. The patient was treated with remdesivir and five days later was negative for the virus. However, sporadic (2-3x weekly) fevers and high inflammatory markers persisted despite a lack of an identifiable source. On the fifth day of illness the patient exhibited a qualitative mental status change with paresthesia and weakness of the left arm. Brain MRI showed no focal abnormalities, while serial EEGs were consistent of an encephalopathy. The symptoms spontaneously resolved after three days. Upon receiving negative bacteriological, virological, mycological, mycobacterial tests and immunological tests, an infectious disease consultant suggested the diagnosis of MIS-A. We administered intravenous immune globulins 5 ml/kg over the course of three days, with intravenous methylprednisolone 80 mg daily. Upon treatment initiation the fevers promptly resolved, with a marked drop of inflammatory markers to normal values within 72 hours. The patient was discharged, and after two months follow up he remains symptom-free and with normal levels of inflammatory markers.

Case 2

A 57 year-old male kidney transplant recipient was transferred to our institution due to fever of unknown origin and a negative extensive work-up at another hospital. Initially, in April 2023, he was diagnosed with mild COVID requiring no specific treatment. However, his fevers persisted (up to 38,7°C) daily despite the resolution of other symptoms. The patient was transplanted

10 years prior due to autosomal dominant polycystic kidney disease, his medical history is remarkable for arterial hypertension, COPD and tertiary hyperparathyroidism. His chronic immunosuppressive regimen is everolimus, mycophenolate and prednisone, other chronic medication include pantoprazol, tamsulosin, allopurinol, lacidipine, moxonidine, urapidil and cinacalcet. An extensive work-up was undertaken, a CT scan of the chest, abdomen and pelvis was remarkable for bone lesions typical of multiple myeloma. Further testing, including a bone biopsy, excluded multiple myeloma and he was diagnosed with a monoclonal gammopathy of unknown significance. Extensive bacterial, virological, parasitological and other microbiological tests came back negative. Laboratory test results were remarkable for persistently elevated C-reactive protein (119-134 ng/ml), erythrocyte sedimentation rate (84 mm/s), fibrinogen and ferritin, however, throughout the stay procalcitonin levels were within normal range. Upon exclusion of infectious causes and a complete hematological work-up, the patient was administered intravenous immunoglobulins (IVIG) (2 g/kg) with methylprednisolone premedication for three days. On the second day of IVIG administration the patient was afebrile and a complete normalization of blood inflammatory markers and a marked improvement in the patient's overall state.

Discussion

We presented two cases of MIS-A in a KTR and a former KTR who both presented with a relapsing fever of unknown origin and persistently elevated inflammatory markers. In both patients the trigger was acute COVID-19, despite having relatively mild symptoms and no requirement of respiratory support. The vast comorbidities and underlying symptoms made the diagnosis challenging and the incidental findings have often led clinicians into additional time-consuming tests. Upon administration of immunoglobulins in both patients the symptoms abated quickly and the laboratory abnormalities markedly improved. Thus far, MIS-A has not been reported in kidney transplant recipients. In this paper we present a patient whose presentation and response to treatment align with MIS-A, however, who does not fit the criteria proposed by the CDC. A potential explanation could be that chronic immunosuppression alters the presentation and thus these patients are undiagnosed for the condition. Only one case of MIS-C in a solid organ transplant recipient is found in the literature, a 3-year old liver recipient[4]. The patient presented with oliguric renal failure, supratherapeutic tacrolimus levels, and hyponatremia, and during the hospital stay also developed a rash, portal vein thrombosis and had dilation of the coronary arteries. The treatment also involved IVIG which resulted in prompt remission of fever and a decrease of inflammatory markers, however, coronary dilation and portal vein thrombosis occurred after treatment. Similar to our patients, cardiac involvement was mild in the context of hemodynamic stability and the patient required no inotropic support or had other evidence of decreased cardiac function. Chronic immunosuppression is postulated to have played a role in the milder disease course. In a study of 15 MIS-A cases by Davogustto et al, cardiovascular involvement was described in 8/15 patients and the overall conclusion of the study is that MIS-A may be more heterogeneous in presentation than previously thought[5]. In our first case, the patient exhibited the full range of criteria with multiple organ involvement (cardiac, neurological, gastrointestinal, immunological), while in the second case chronic immunosuppression may have altered the presentation. The response to treatment may indicate a hyperimmune response to acute COVID-19 as the cause in both cases. Lack of cardiac involvement in chronically immunosuppressed patients should not defer clinicians from suspecting MIS-A. Chronic immunosuppression, however, leads to a risk of atypical infections, atypical presentations or malignant diseases which may present similar to MIS-A, requiring meticulous testing and exclusion of infectious, immunological and malignant causes of fever of unknown origin. Treatment of MIS-A includes corticosteroids or IVIG, however, management of immunosuppression in transplant patients remains unclear. We did not opt for a change in immunosuppression and have decided to administer corticosteroids and IVIG with good outcomes in both cases.

Conclusion

We presented two cases of MIS-A following COVID-19, one in a former KTR with no immunosuppression who developed the full MIS-A phenotype, and one in a KTR in whom chronic immunosuppression may have altered disease presentation. Treatment with corticosteroids and IVIG achieved good outcomes with prompt resolution of symptoms and inflammatory parameters.

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