

# An unusual case of distributive shock

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## ABSTRACT:

- **Background:** Kaposi sarcoma inflammatory cytokine syndrome (KICS) is a condition affecting HIV-positive individuals infected with Kaposi sarcoma herpesvirus. It was recently described and only few cases have been reported in the literature so far. In this syndrome, cytokine dysregulation, primarily IL-6, is responsible for amplifying systemic response leading to distributive shock.
- **Case Report:** This report illustrates a rare cause of distributive shock with fever, severe intravascular haemolysis and diffuse rash in a HIV-patient. The main difficulty concerning correct diagnosis and therapy was the differential diagnosis and the patient's necessity to receive urgent intensive medical treatment. Why should an emergency physician be aware of this? This clinical case reminds physicians that there are some critical illnesses, like KICS, affecting HIV-positive patients, which present as a distributive shock with fever but are different from sepsis and require a specific treatment.
- **Keywords:** Distributive shock, Kaposi sarcoma herpesvirus (KSHV), Interleukin 6 (IL-6), Doxorubicin.

## INTRODUCTION

The pathophysiology of shock recognizes four distinct mechanisms classified into four broad categories: hypovolemic, cardiogenic, obstructive, and distributive<sup>1</sup>. Table 1 outlines the causes of shock within the Weil and Shubin classification system. Distributive shock is correlated by a loss of vasomotor control producing arteriolar and venular dilation, characterized by increased cardiac output with decreased systemic vascular resistance generating hypotension, multi-organ failure and generalized oedema due to the leakage of fluids from capillaries into the surrounding tissues<sup>2</sup>. In most cases, inflammatory mediators and cytokines release play a major role in the development of distributive shock-inducing systemic vasodilation and capillary leak, further complicating the clinical picture. Due to the complexities of this disorder, the causes and treatments for distributive shock are multimodal<sup>3</sup>. The following case report illustrates a rare cause of distributive shock with fever, severe intravascular haemolysis and diffuse rash in an HIV-patient. The coexistence of these different clinical entities makes it difficult to rule out the correct diagnosis from sepsis, drug reaction with sepsis, drug reaction with eosinophilia and systemic symp-

toms (DRESS)<sup>4</sup>, staphylococcal toxic shock syndrome, viral haemorrhagic fever<sup>5</sup>, acute adrenal insufficiency, anaphylaxis<sup>6</sup>, and idiopathic capillary leak syndrome (ISCLS). All the life-threatening disorders above-mentioned are characterized by hypotension, multi-organ failure and generalized oedema due to the leakage of fluids from capillaries into the surrounding tissues<sup>7</sup>.

The factors leading to vasodilation and shock are multimodal and complex. A careful history and physical examination to elucidate the underlying cause and multi-system approach to treatment is strictly required. We report a case of Kaposi sarcoma inflammatory cytokine syndrome (KICS) and review its characteristics to increase the awareness of this important diagnosis, whose morbidity and mortality rates are very high.

## CASE REPORT

A young man was admitted to the Emergency Department (ED) for fever, sore throat and generalized malaise. He had previously been in good health except for lobar pneumonia treated with antibiotic therapy at home in 2011, endoscopic thoracic sympathectomy for hyperhidrosis in 2012, left inguinal hernia surgery complicated

**Table 1.** The four pathophysiological types of shock and the causes.

Pathophysiological type	Cause
Hypovolemic	Hemorrhage, trauma, dehydration
Cardiogenic	Myocardial infarction, cardiomyopathy, valvular disease, severe arrhythmias
Obstructive	Pulmonary embolism, tamponade, aortic dissection

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by surgical site infection treated with antibiotic therapy and vacuum-assisted closure therapy in 2016 and removal of an anal acuminata condyloma in June 2018. He had recently found out he was human immunodeficiency virus (HIV) positive. The patient was a non-smoker, not a user of illicit drugs and he had no known allergies. On examination the patient's mental status was normal, blood pressure 135/75 mmHg, heart rate 115 beats per minute, respiratory rate 18 breaths per minute, oxygen saturation 96% while breathing ambient air and temperature 38.3°C. Physical examination revealed active Kaposi Sarcoma skin lesions already present for some months, axillary and inguinal polyadenopathy, moderate hepatosplenomegaly and lower limbs swelling.

Laboratory-tests were notable for a C-reactive protein (CRP) at 17.3 mg/dL (normal value <0.5), a procalcitonin 1.7 ng/mL (normal value <0.5), a white-cell count of  $6.95 \times 10^9/L$  (reference range, 4 to 10) with a CD 4 count of 294 cell/micro (range 500-1,500), a red blood cell count of  $3.34 \times 10^9/L$  (reference range, 4.4 to 6), haemoglobin of 8.4 g/dL, lactate dehydrogenase 150 U/L (reference range 100-180 U/L), platelet count of  $95 \times 10^9/L$  (reference range, 140 to 440), a lactate level of 2 mmol/L while the blood electrolytes were normal as were the results of tests of coagulation profile, and of renal and liver function. Blood cultures were negative while testing was positive for viral genomes: HIV-1 RNA at 2.649.032 copies/mL, Epstein Barr virus (EBV) 767 gEq/mL, Cytomegalovirus (CMV) 45 copy/mL and Kaposi sarcoma herpesvirus (KSHV) at 80.072 copies/mL. He was admitted to the Infectious Disease Unit and was treated with antiretroviral therapy (ART): darunavir 800/150 mg and emtricitabine 200/10 mg per os/die.

Esophagogastroscopy and colonoscopy were performed in consideration of unexplained anaemia, showing Kaposi Sarcoma nodular lesions then confirmed with a biopsy (Fig. 1). Chest and abdomen CT scan showed enlargement of submandibular, later cervical, axillary (Fig. 2), ilo-mediastinal, abdominal-pelvic lymph nodes and splenomegaly (longitudinal diameter 15 cm) besides bilateral pleural effusion, and ascites. One week after admission, the patient's clinical status deteriorated: the anaemia worsened (haemoglobin value of 5 g/dL despite multiple transfusions) and a diffuse red skin rash appeared, associated to respiratory failure, tachycardia, hypotension, and anasarca. The level of procalcitonin rose to 4.9 ng/mL, lactate dehydrogenase up to 1700 U/L, and bilirubin 2.8 mg/dL.

The patient was transferred to the Sub-intensive Care Unit: in the hypothesis of haematological malignancy or hemophagocytic syndrome or drug-mediated haemolytic anaemia, ART was stopped for 48 h, immunoglobulin iv (35 g/day) was prescribed for two days, and methylprednisolone (1 g/day) for three days. Bone marrow aspiration showed the presence of hypoplasia and dysplasia of the erythroid series with no evidence of pathological infiltration or hemophagocytosis. The histological analysis of one axillary lymph node biopsy confirmed Kaposi Sarcoma infiltration and the presence (in mantle zone cells) of Human herpesvirus-8 (HHV-8) by immunohistochemistry.

The consultation with an infectious and haematological disease expert made Kaposi sarcoma inflammatory cytokine syndrome (KICS) the most likely diagnosis, so chemotherapy with Liposomal doxorubicin was intravenously administered and ART, with emtricitabine 200/100 mg and dolutegravir 50 mg was prescribed. Quantitative levels of serum human interleukine-6 (hIL-6) were not detected because the assay was not available in our hospital laboratory.

The patient's condition progressively improved with resolution of fever and respiratory distress, with the reduction of peripheral lymphadenopathy dimensions, and complete recovery of anasarca and skin red rash. The patient was therefore transferred to the Infectious Diseases Unit to continue medical treatment.



**Figure 1.** Esophagogastroscopy and colonoscopy were performed in consideration of unexplained anaemia, showing Kaposi Sarcoma nodular lesions then confirmed with biopsy.



**Figure 2.** A-B, A CT of the body detected enlarged lymph nodes in particular in submandibular, later cervical and axillary regions.

## DISCUSSION

The main difficulty concerning the diagnosis was the coexistence of: distributive shock with fever, severe intravascular haemolysis, and diffuse rash. The medical history and clinical examination provided the first clues. The general deterioration and worsening anaemia that occurred a few days after admission to hospital and taking antiretroviral therapy, made the hypothesis of Immune Reconstitution Inflammatory Syndrome (IRIS) less likely. Furthermore, the normal range for complement C3-C4 blood test and the absence of a response to intravenous immunoglobulin (IVIg) and to high dose steroid ruled out immune-mediated anaemia. Could it be a case of drug-induced toxicity? The first decision to stop darunavir (a protease inhibitor that contains a sulphonamide moiety) gave us great hope by improving the anaemia and the resolution of skin rash.

Blood and urine cultures were negative, no other source of infection supported an infectious disease, hence, despite the persistent high fever and severe inflammatory response

(with acute phase biomarkers elevation, procalcitonin included), we held firm not to give antimicrobial or anti-fungal therapy. The absence of urticaria, itching, tongue angioedema, wheezing, and eosinophilia made DRESS syndrome less likely<sup>8</sup>; normal urinary free cortisol, plasma corticotropin, and plasma cortisol measurements ruled out adrenal insufficiency; the diagnosis of idiopathic capillary leak syndrome seemed to be excluded by persistent hyperpyrexia and the absence of monoclonal gammopathy<sup>9</sup>.

The rapid clinical deterioration required a refinement of the differential diagnosis: disseminated Kaposi's sarcoma herpesvirus (KSHV or HHV-8) and the related disorders including multicentric Castleman's disease (KSHV-MCD), Kaposi Sarcoma Herpesvirus Inflammatory Cytokine Syndrome (KICS), and primary effusion lymphoma (PEL) must be excluded<sup>10-11</sup>.

The excisional biopsy of the axillary lymph node and the bone marrow biopsy and aspiration ruled out lymphoproliferative disorder and hemophagocytic lymphohistiocytosis.

To our knowledge cytokines storm enhances the systemic response in MCD and KICS: plasma IL-6 level should be measured to sustain this diagnosis<sup>12</sup>.

KICS is a rare newly described condition-affecting individuals who are HIV-positive and are infected with Kaposi sarcoma herpesvirus (or human herpesvirus 8). The onset of this syndrome seems to be like severe sepsis with acute respiratory distress and shock that need ventilatory and vasopressor support, with the difference that antibiotics have no benefit.

KICS appears with non-specific symptoms: fever, fatigue, oedema, cachexia, respiratory symptoms, gastrointestinal disturbances, arthralgia, myalgia, altered mental state, and neuropathy with or without pain. Laboratory abnormalities include anaemia, thrombocytopenia, hypoalbuminemia, and hyponatremia; radiological abnormalities include lymphadenopathy, splenomegaly, hepatomegaly, and body cavity effusion. Plasma levels of viral IL-6, human IL-6, human IL-10, and HHV-8 genomes are significantly higher<sup>13</sup>. KICS and MCD have similar clinical features but a different histologic pattern. In KICS, in fact, the lymph node is characterized by KS infiltration or reactive hyperplasia, whereas in MCD the lymph node usually shows hypocellular germinal centers and KSHV-infected, polyclonal plasmacytoid cells in the interfollicular area<sup>14</sup>.

To date, there are no standard therapies for KICS. Pathophysiology resembles KICS, hence efforts have been made to treat KICS's patients with therapeutic protocols for MCD, including rituximab and liposomal doxorubicin or high-dose zidovudine and valganciclovir<sup>15,16</sup>.

Morbidity and mortality rates are very high in patients with KICS. In Uldrick's retrospective case series, 50% (3 out of 6) of the patients died within 3 to 7.5 months<sup>17</sup>.

## CONCLUSIONS

This clinical case describes the complicated interrelationship between immunity, virology, and tumour biology. Furthermore, clinicians must remember KICS

as a possible cause, in seropositive patients, of distributive shock and fever different from sepsis, in which an antimicrobial therapy could have more adverse effect without bringing any benefits in term of the outcome. Clinicians must be aware of this clinical illness, poor prognosis, and complexity, requiring a multidisciplinary approach to give appropriate treatment and management.

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#### INFORMED CONSENT:

Author has tried but failed to obtain consent and the paper is to be anonymised to make sure that no mention of specific gender or age is present in the paper.

#### CONFLICT OF INTERESTS:

The authors declare that they have no conflict of interest.

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