CLINICAL IMAGE

DRESS syndrome after KRd (carfilzomib, lenalidomide, dexamethasone) therapy in a patient with multiple myeloma

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A 67-year-old man with multiple myeloma (immunoglobulin A lambda type, stage II according to the International Staging System) was admitted to the hospital for a continuation (second cycle) of KRd therapy (carfilzomib 27 mg/m^2 intravenously, lenalidomide 25 mg/d, dexamethasone 40 mg/d); it was day 15 of the 28-day cycle. On admission, the patient reported high fever, excessive sweating, fatigue, and loss of appetite. On physical examination, lymphadenopathy as well as nonpruritic, maculo-papular rash covering more than 50% of the skin were found (FIGURE 1A).

Laboratory tests showed leukocytosis (21.3×10^9/l; reference range, $3.9–9.5 \times 10^9$/l) with 25% of atypical lymphocytes in peripheral smear, eosinophilia (5.98×10^9/l; reference range, $0.03–0.29 \times 10^9$/l), anemia with a hemoglobin level of 11.9 g/dl (reference range, 13.2–16.6 g/dl), thrombocytopenia (60×10^9/l; reference range, $149–303 \times 10^9$/l) as well as elevated levels of alanine aminotransferase (263 U/l; reference range, 0–41 U/l), aspartate aminotransferase (94 U/l; reference range, 0–37 U/l), bilirubin (3.4 mg/dl; reference range, 0–1.2 mg/dl), alkaline phosphatase (263 U/l; reference range, 40–129 U/l), and C-reactive protein (6.3 mg/dl; reference range, 0–0.8 mg/dl).

The abdominal ultrasound and echocardiogram were normal. Infections with hepatitis B and C viruses (HBV and HCV), cytomegalovirus (CMV), human herpes type 6 virus (HHV-6), Epstein–Barr virus, and HIV were excluded. Antinuclear and anti–double-stranded DNA antibodies were negative. A skin biopsy was performed and on histopathological examination, an intense inflammatory reaction was found combining several histopathological patterns described in drug reaction with eosinophilia and systemic symptoms (DRESS; including eczematous, lichenoid, perivascular and leukocytoclastic) (FIGURE 1B).[1]

DRESS syndrome was diagnosed, with 8 out of 9 points in the Registry of Severe Cutaneous Adverse Reactions scoring system: fever exceeding 38.5 °C (0); enlarged lymph nodes (1); eosinophilia (2); atypical lymphocytes (1); skin rash covering more than 50% of the body surface area (1); skin rash suggesting DRESS (1); biopsy suggesting DRESS (0); organ involvement (liver) (1); rash resolution in 15 days or more (0); and negative viral titers (HCV/HBV) (1).[1-3]

The hematological treatment was discontinued and prednisolone 1 mg/kg/d was started. After 5 days of therapy no improvement was observed. Intravenous immunoglobulins (IVIg) 0.5 g/kg/d were administered and continued for 4 consecutive days, leading to a gradual regression of the skin lesions and normalization of liver enzymes (FIGURE 1C).

Unfortunately, on the 10th day since admission the patient had contact with a person diagnosed with COVID-19. He tested positive for SARS-CoV-2 infection and developed COVID-19 pneumonia. Convalescent plasma and intravenous dexamethasone were administered. A week later, CMV infection (DNA CMV viral load, 26 807 cp/ml) was detected and despite severe thrombocytopenia, which was thought to have been exacerbated by the infection itself, ganciclovir was initiated. Pulmonary inflammation gradually resolved and CMV viral load decreased significantly.

DRESS syndrome, also known as drug-induced hypersensitivity syndrome, is a severe, potentially life-threatening adverse drug reaction characterized by a rash with high fever, eosinophilia,

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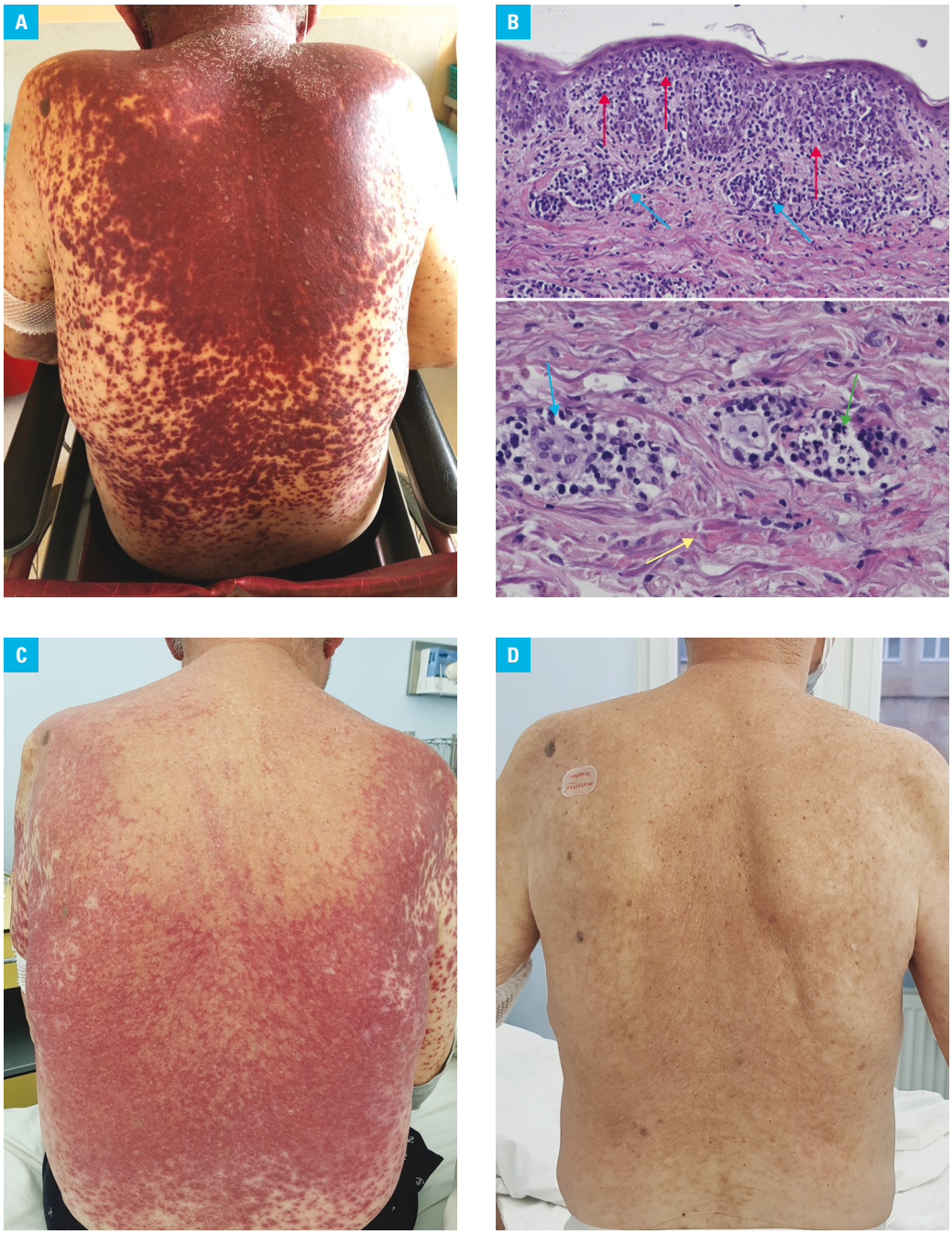

FIGURE 1 **A** – a photo of the skin lesions just before therapy with intravenous immunoglobulins: disseminated, grouped, and confluent papules turning from erythematous into hemorrhagic; **B** – histopathological examination of the skin biopsy specimen revealing a coexistence of lichenoid-like (upper panel, red arrows) and perivascular dermatitis (blue arrows) in the upper dermis. Swelling of endothelial cells, focal nuclear debris (lower panel, green arrow), and extravasation of red blood cells (lower panel, yellow arrow) around the vessels can be seen (hematoxylin and eosin staining; magnification × 20 for upper panel and ×40 for lower panel). **C** – gradual healing of the lesions during treatment; **D** – remission of the lesions with postinflammatory hyperpigmentation one month after treatment initiation

and systemic organ involvement. The mortality rate is around 10%. In the course of the disease, viruses such as HHV-6, CMV, or HBV can be reactivated. CMV reactivation in our patient developed only after resolution of the skin and liver abnormalities, leading to exacerbation of anemia and thrombocytopenia.

DRESS syndrome occurs usually about 4 weeks after exposure to the culprit drug. In our patient, the skin lesions first appeared during the 7th week of KRd therapy. Lenalidomide in KRd seems to be the most probable causative medication, either alone or in combination with carfilzomib. There are no reports of DRESS induced by carfilzomib alone. Lenalidomide is being increasingly used in hematological therapy but only a few cases of related DRESS have been published. The presented case is the first report of KRd-induced DRESS in the Polish population. Treatment of DRESS may be challenging. In our patient, IVIg infusions resulted in remission of the skin lesions (FIGURE 1D) and a decrease in liver

injury markers. Additionally, IVIg along with convalescent plasma may have prevented a potentially severe COVID-19 in our patient with a hematologic malignancy.[4,5]

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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