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LETTER TO THE EDITOR

Dramatic neurological debut in a case of Köhlmeier-Degos disease

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Dear Editor,

Köhlmeier-Degos disease (KDD) is a rare thrombo-obliterative vasculopathy involving small- and medium-caliber vessels [1, 2]. Less than 200 cases have been reported and a possible genetic predisposition has been suggested [3]. Vasculitis, endothelial dysfunction, and hyperactivation of complement and coagulation factors are the proposed mechanisms. The disease typically starts between the third and the fifth decade involving the skin with pathognomonic papules surrounded by a telangiectasic rim. In almost 50% of cases, the vasculopathy involves other tissues and organs, such as the gut, lungs, and central nervous system (CNS) with possible fatal complications, hence the definition of malignant atrophic papulosis. We hereby describe a peculiar case of KDD with neurological debut, rapid fatal outcome, and unusual neuropathological findings.

A 44-year-old male affected by diabetes mellitus and HCV-related chronic hepatitis sub-acutely manifested right-sided weakness with progressive gait difficulties following a cycle of interferon therapy. At the same time, he received a diagnosis of KDD because of the appearance of erythematous, ulcerating papules on trunk and limbs. Three months later, because of the progressive worsening of the weakness, which spread to all his limbs, the patient was admitted to our unit. He appeared awake but erratically confused; neurological examination evidenced severe tetraparesis with discrete right spasticity, bilateral Babinski sign, and meningeal syndrome. MRI showed widespread T2-hyperintense lesions in the mesencephalic tegmentum, dorsal vermis, bilateral thalami, splenium of corpus callosum, left parahippocampal cortex, and paracentral lobule. Diffuse leptomeningeal enhancement was present following gadolinium administration (Fig. 1a–d). Cerebrospinal fluid (CSF) analysis revealed mild pleocytosis with increased proteins and high albumin index (9.7). An important inflammatory state was present (CRP 6.95 mg/dL) without evidence of bacterial infection. Herpesvirus and all retroviral infections were excluded based on serum and CSF assays. Despite treatment with intravenous steroids and immunoglobulins, patient's conditions rapidly worsened: he became aphasic, tetraplegic, and finally went into a coma state. He died by cardiopulmonary failure 1 week after hospitalization. At autopsy, a picture consistent with perivenous lymphocytic meningoencephalitis was found in association with laminar necrosis of cortical neurons, but with no evidence of either ischemic or hemorrhagic lesions due to direct vascular involvement (Fig. 1e–h). This observation underlines the rule of perivascular spaces as a possible pathway of infections spread [3]. Additional findings were infiltrative myocarditis and polyserositis.

CNS involvement is not a common systemic manifestation of KDD [4], but, when present, it always represents an expression of dramatic outcome. Previous studies have reported a pattern of neurological involvement mainly consisting of ischemic or massive hemorrhagic strokes, due to thrombo-obliterative alterations of small- and medium-caliber vessels [5, 6]. Hereby, we report for the first time, instead, a very early neurological debut, substantially simultaneous with the dermatological manifestations, with a rapidly progressive inflammatory involvement of the brain and leptomeninges. In particular, the neuropathological study showed an inflammatory process involving

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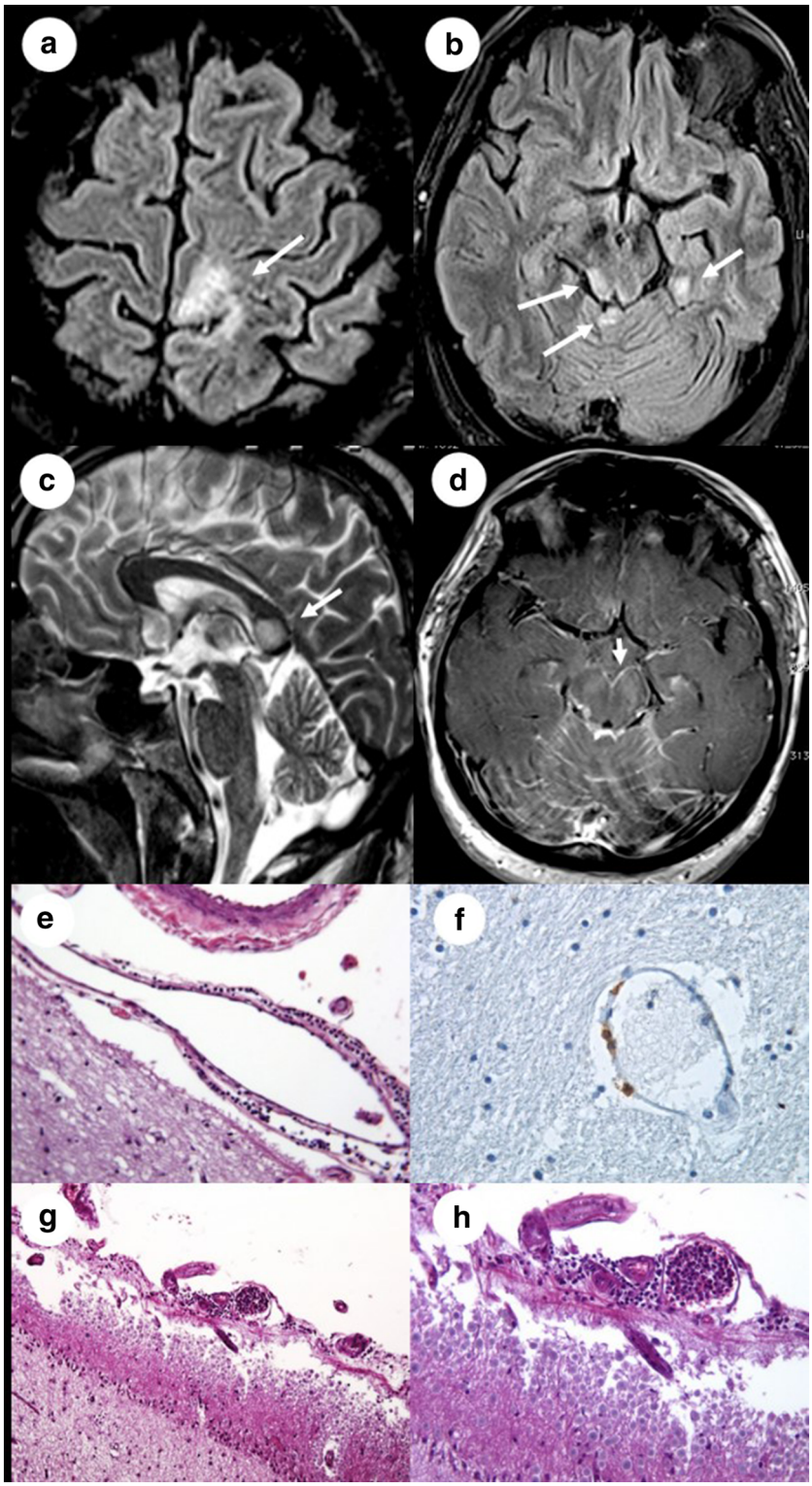

Fig. 1 Brain MRI. Axial FLAIR-weighted (**a**, **b**), sagittal SE T2-weighted (**c**), and axial SE T1 post-gadolinium-weighted (**d**) sequences. Axial FLAIR MRI sequences show several lesions, namely in the paracentral lobule (**a**) (arrow), right mesencephalic tegmentum, dorsal vermis, left parahippocampal cortex (**b**) (arrows), and splenium of corpus callosum (**c**) (arrow). Axial SE T1 post-gadolinium contrast MRI (**d**) readily shows diffuse leptomeningeal enhancement (**d**) especially at the ventral surface of both pons and midbrain, along with obliteration of quadrigeminal cistern (arrowhead). At autopsy, examination of the CNS revealed diffuse perivenous lymphocytic meningoencephalitis with few scattered $CD20^{+}$ lymphocytes throughout the parenchyma and the vessel wall (**e**, **f**); laminar necrosis of cortical neurons with accumulation of glycogen, congestion of neocortical vessels, and neutrophil infiltrates was evident (**g**, and higher magnification in **h**). *No evidence of viral particles or nucleic acid was found. H&E, hematoxylin and eosin* (**e**,**g**,**h**); *EP495Y, anti-CD20 antibody* (**f**).

the parenchymal and leptomeningeal venules, configuring a picture of aseptic meningoencephalitis. The presence of lymphocytic infiltrates let us suspect a viral infection, but no evidence of viral particles or nucleic acids was found. Unexpectedly, we did not find thrombotic occlusion of the small brain arteries, nor thickness of vessel wall, nor significant endothelial pathology. Clinically, before the negativity of serum and CSF microbiological analyses, the

phenotype suggested a distinct neurological disease, possibly a viral meningoencephalitis, not associated but overlapping the KDD. However, we did not find any alternative cause in our patient responsible for his unusual meningoencephalitis. Our case then represents, to the best of our knowledge [5, 7], the first evidence that KDD itself may cause a dramatic inflammatory response triggering massive neuronal death in cerebral cortex and extensive involvement of the adjacent leptomeninges.

In conclusion, KDD is a potentially life-threatening disease, especially when it determines rapid and severe involvement of "noble" tissues such as the CNS [7]. In our case, the vasculitis itself likely caused aseptic leptomeningeal inflammation and multifocal encephalitis, without significant thrombotic or hemorrhagic phenomena, thus leading to dramatic neurological deterioration. Therefore, our report paradigmatically highlights the under-recognized relationship between KDD and meningoencephalitis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical statement All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration.

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