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CASE REPORT

Multiple acute ischemic strokes as the onset manifestation of acute promyelocytic leukemia

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Acute promyelocytic leukemia often manifests with hemorrhagic diathesis, thrombotic events being much rarer. This is the case of a 59-year-old patient with thrombotic cerebro-vascular complications as the onset manifestation of acute promyelocytic leukemia.

Keywords: multiple ishemic strokes, acute promyelocytic leukemia, leukemia.

INTRODUCTION

Acute promyelocytic leukemia (APL) represents a distinct subtype of acute myeloid leukemia (AML), being characterized by variable morphologic, immunophenotypical, and clinical features, characteristic cytomorphology, and abnormal promyelocytes [1]. APL often manifests with hemorrhagic diathesis [2], thrombotic events being much rarer [3].

CASE REPORT

This is the case of a right-handed, 59-year-old patient with no significant pathological history, who was admitted to our clinic for a left-sided hemiparesis and anomia with sudden onset (about 24 hours prior hospital admission). *Clinical examination* was normal. Temperature was 38°C. *On neurologic examination* the patient was alert, oriented to person, place and time, with *left* central facial paresis, left hemiparesis, and anomic aphasia.

Cerebral CT showed an acute right frontal-subcortical lacunar infarct. Because the clinical picture could not be entirely explained by the lesion visible on cerebral CT, *MRI diffusion weighted imaging* was performed and revealed scattered foci of high signal in the right fronto-insular, parietal regions (Fig. 1) and left temporal region (Fig. 2).

The *electrocardiography* revealed sinus rhythm, HR 62 bpm, with no anomalies. *Ultrasound examination of carotid and vertebral arteries* revealed only linear hyperechoic atheroma plaques on left internal carotid artery, without stenosis.

Laboratory tests revealed severe pancytopenia (hemoglobin level (Hb) was 5.92 g/dL, total leukocyte count was 642/μL, and platelets were 21200/μL). Coagulation profile reported prolonged prothrombin time (16.3s) with abnormal activated partial thromboplastin time (66%), and the international normalized ratio was 1.32. D-Dimer level was also raised (14.20 μg/mL).

Given the ongoing persistent fever and the proneness to infections of the pancytopenic patients, the possibility of a septic multiple cerebral embolism was considered. We performed a transthoracic echocardiography (repeated during the first 7 days) that revealed no valvular vegetations (which might have suggested infectious endocarditis). Moreover, the blood cultures were negative and the pulmonary and urinary screening tests (chest x-ray, urinalysis and urine cultures) did not show any infection. Peripheral blood smear showed 88% abnormal hypergranular promyelocytes and 10% lymphocytes. Flow cytometry was positive for CD13, CD33, and CD117 and negative for CD34, HLA-DR, CD11b. The genetic testing for PML-RARα (promyelocytic leukemia-retinoic acid receptor alpha) mutation was not performed.

Taking into consideration the clinical features and peripheral blood morphology we started immediatly the treatment with all-trans retinoic acid (ATRA) (dose of 45 mg/m^2) and idarubicin, transfusion of platelets, red blood cells and clotting factors (fresh frozen plasma) in accordance with

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the established guidelines for APL [4], taking into account the potential risk for hemorrhagic complications.

The induction treatment led to complete remission. Cerebral CT follow-up at 4 months showed only ischemic sequelae of previous stroke in the superficial territory of middle cerebral arteries (Fig. 3) and the neurological examination was favorable (without significant motor deficits or language impairment).

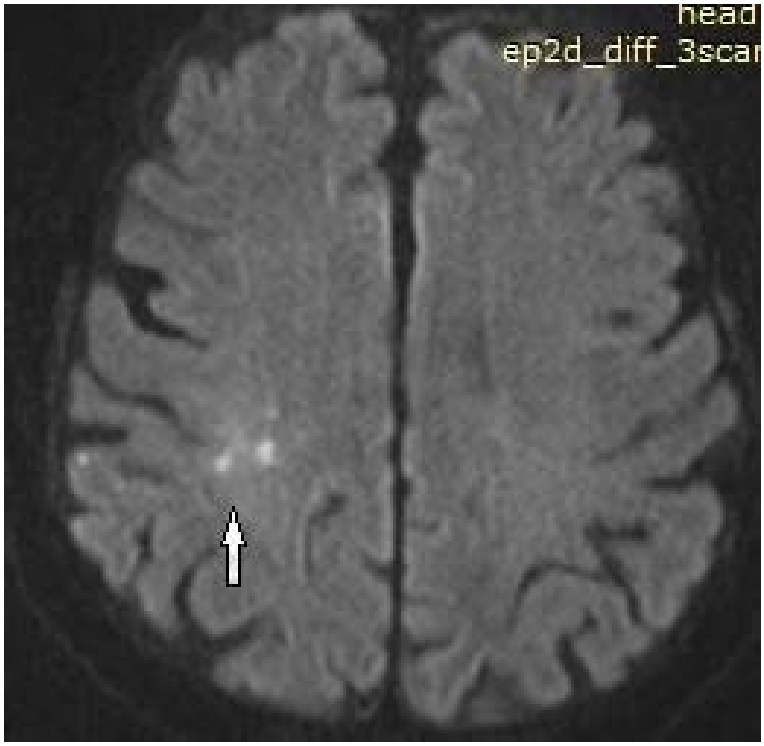

Figure 1. MRI axial diffusion-weighted image - scattered foci of high signal in the right parietal region.

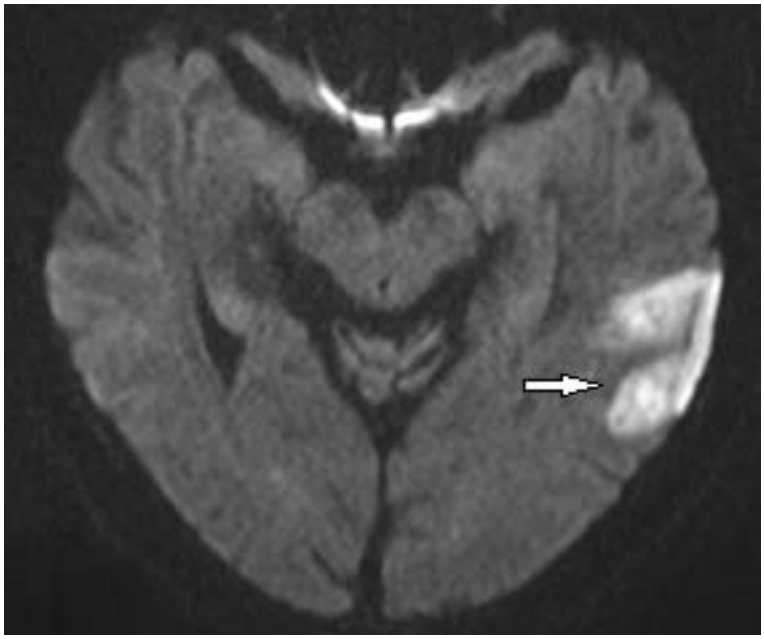

Figure 2. MRI axial diffusion-weighted image - high signal in the left cortico-subcortical temporal region.

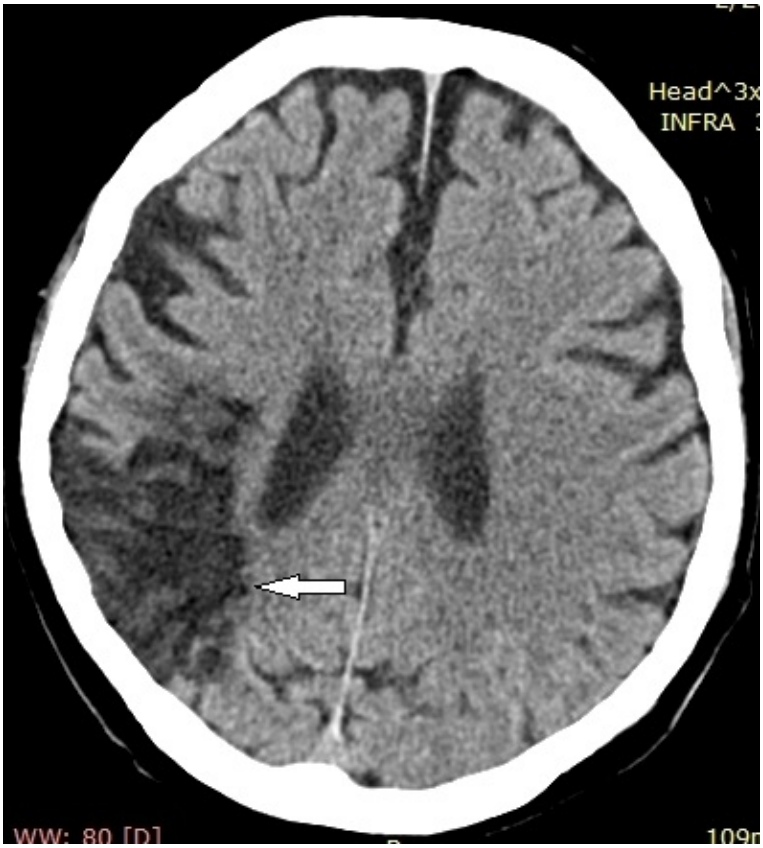

Figure 3. Noncontrast CT at 4 months demonstrates a large right middle cerebral artery distribution infarction.

DISCUSSION

There are only a few cases in the literature of thrombotic vascular complications as the onset manifestation of AML (the vascular injury was limited to one arterial territory) [5-7]. In a case series of twenty-four patients, thrombotic events were the first clinical manifestation of leukemia in only 3.4% of cases [8]. Other reported cases presented with coronary thrombotic events [9], deep vein thrombosis, pulmonary thromboembolism [10] or infarctions of other organs [11]. Cerebral involvement in patients with active AML, although relatively rare, is associated with a 5 times higher mortality risk [12].

AML coagulopathy is thought to be the result of several intricate factors: activation of extrinsic pathways of coagulation due to the release of procoagulant substances from neoplastic cells [13], increase of annexin II receptor expression on the surface of leukemic promyelocytes responsible for binding plasminogen and tissue plasminogen activator and resulting in increased thrombin formation [14] and expansion of proteolysis phenomenon [13]. It has been observed that sometimes the initiation of ATRA treatment may be involved in generating the prothrombotic status, although in all cases the purpose of the treatment is to reverse coagulopathy. ATRA therapy can disrupt the balance between the procoagulant and fibrinolytic properties of leukemic promyelocytes, therefore leading to thrombotic events [10].

The particularities of this case are, on the one hand, the thrombotic damage in more than one arterial territory and, on the other hand, the appearance of these lesions before initiation of treatment with ATRA (and not after as is usually the case).

CONCLUSIONS

In our patient the ischemic stroke due to multiple thrombotic occlusions of intracranial vessels in the context of disseminated intravascular coagulopathy was the first manifestation of the disease prior to the initiation of ATRA treatment. Vascular occlusion as a first clinical manifestation of APL can be a serious complication independently of

ATRA. Although several mechanisms have been posited, there is currently no certain explanation for the thrombotic complications of APL. Although in most of the published cases the prognosis was poor, the clinical evolution of our patient was remarkably good (no major neurological deficits).

Conflict of Interest disclosure. The authors declare that there are not conflicts of interest.

Leucemia acută promielocitară se manifestă de obicei cu diateze hemoragice, manifestările trombotice fiind mult mai rare. Descriem cazul unui pacient în vârstă de 59 ani cu afectare trombotică cerebro-vasculară ca manifestare de debut a leucemiei acute promielocitare.

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