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Watershed Infarctions and Hypereosinophilic Syndrome Secondary to Metastatic Lung Cancer: A Case Report

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Abstract: Watershed infarcts are traditionally attributed to ischemia caused by hypoperfusion, with or without vessel stenosis. Implicated diseases usually include atherosclerosis, congestive heart failure, hypotension, angiitis, and less commonly, sickle cell disease. In this report, we present an uncommon case of diffuse watershed infarctions possibly caused by reactive (secondary) hypereosinophilic syndrome. We also discuss the definition and causes of hypereosinophilic syndrome and its neuroradiologic manifestations.

Keywords: Hypereosinophilic syndrome, stroke, watershed areas infarctions

Case presentation

A 33-year-old man with known lung cancer that metastasized to both lungs, the liver, and the adrenal glands presented to the emergency department with diabetic ketoacidosis. Several days after hospitalization, the patient developed altered mental status and was unable to answer questions. Computed tomography (CT) of the brain showed several areas of cerebellar hypodensity that were initially perceived as artifacts. However, on re-evaluation of his neurologic status, the patient demonstrated areflexia in the right upper extremity and Babinski signs. Therefore, magnetic resonance (MR) imaging of the brain was performed for further stroke workup. The examination revealed innumerable new acute bilateral infarctions in the cerebral and the cerebellar hemispheres as well as in the brainstem in the predominantly watershed areas, with possible presence of superimposed emboli (Figure).

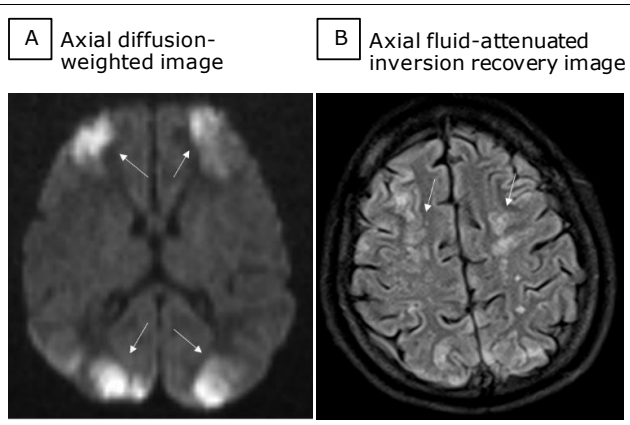
The patient did not develop hypotension or atrial fibrillation during hospitalization. Brain MR angiography did not show any significant intracranial artery stenosis. An echocardiogram obtained 3 days prior to the MR examination revealed only primary pulmonary hypertension. Laboratory studies did not show any evidence of hypercoagulability.

Key Points

- Watershed areas of the brain are the regions between 2 perfusion territories, which are at risk for ischemia in the setting of hypotension.
- Hypereosinophilic syndrome is characterized by hypereosinophilia (> 1500 cells/μL) with end organ damage and is a rare cause of watershed infarcts and pseudotumors.
- Hypereosinophilic syndrome should be considered in a patient with a history of malignant tumor and without other cause of watershed infarcts. This is especially important when the watershed infarcts are diffuse, indicating that they are not due to hypotension across a specific vascular territory.

Given the patient's lung cancer, tumor emboli were also considered as a possible cause of watershed infarcts, but chest CT did not indicate invasion of the tumor into the pulmonary veins. Initial lung cancer workup revealed leukocytosis, white blood cell (WBC) count of 46 000/μL (normal range, 4500-10000/μL, Olive-View Medical Center) with 19 910/μL eosinophils (normal range, 0-400/μL, Olive-View Medical Center). The patient did not have a history of allergies or helminth infection. A peripheral blood smear did not show any immature blood cells. Genetic testing did not detect a *BCR-ABL* gene mutation. However, when the patient developed watershed infarctions and altered mental status, his WBC count was elevated to 111000/μL with 60590/μL eosinophils. Eventually, because of the patient's poor neurologic status and advanced malignant tumor, the patient's family elected hospice care.

Figure. Brain MRI Demonstrating Watershed Infarcts in a 33-year-old Patient with Hypereosinophilic Syndrome.



A, B. Axial diffusion-weighted image (DWI) (1A) of the brain demonstrates multiple bilateral infarcts in the anterior and middle cerebral arteries watershed areas (A, arrows). Axial fluid-attenuated inversion recovery (FLAIR) image (1B) of the brain demonstrates corresponding hyperintense areas consistent with infarcts (B, arrows).

Discussion

Watershed areas lie between 2 nonanastomosing neighboring vascular territories at the borders of the anterior, the middle, and the posterior cerebral arteries.[1] Ischemia in the watershed areas is often a result of hypotension associated with atherosclerotic plaques, congestive heart failure, vasculitis, or sickle cell disease.[2,3]

According to Mangla et al,[1] perfusion imaging in acute stroke exhibits multiple patterns of perfusion deficits. The authors suggested that patients who presented with watershed infarctions due to transient hypotension might revert to normal perfusion in the brain after normalization of their blood pressure. The authors also noted that infarcts due to multiple emboli may show matched decreased perfusion and restricted diffusion areas, which may subsequently reperfuse, the sign of higher probability of patient recovery.[1] Patients with severe arterial stenosis or occlusion may exhibit a diffusion-perfusion mismatch with decreased perfusion throughout a vascular territory; this pattern increases the risk of subsequent strokes.[1]

Furthermore, Mangla et al[1] observed two stages in hemodynamic impairment. In the first stage, decreased cerebral perfusion pressure resulted in compensatory cerebral vasodilation. On perfusion imaging, these areas showed increased cerebral blood volume and mean transit time.[1] In patients whose hemodynamic is already compromised by maximal vasodilation, unlike in healthy individuals, acetazolamide challenge revealed no increase in cerebral blood flow.[1] In stage II of hemodynamic impairment, as Mangla et al[1] argued, cerebral perfusion pressure decreased beyond adaptive capacity of vasodilation so that the resulting decrease in cerebral blood flow may force the brain to increase oxygen extraction. This phenomenon, known as "misery perfusion," is a sign of an increased risk of recurrent stroke.

When common causes of watershed infarction are ruled out, rare causes such as hypereosinophilic syndrome (HES), defined as hypereosinophilia with evidence of organ damage by eosinophils,[4,5] should be considered. Based on the causes of hypereosinophilia, HES can be seen as a result of primary (eg, myeloproliferative neoplasm), secondary (eg, helminth infection, neoplastic disease), or idiopathic causes.[5,6] Documented neurologic manifestations of HES include peripheral polyneuropathy, encephalopathy, inflammatory pseudotumor, and strokes.[7,8] The diagnosis of HES requires exclusion of other more common causes of organ damage even in the presence of hypereosinophilia.[4] In our patient, other possible causes of stroke were ruled out, and therefore his stroke was attributed to hypereosinophilic syndrome.

As described in the literature,[1,9] the propensity of microemboli of certain sizes to lodge in the watershed areas is possibly caused by hypoperfusion that impairs clearance of microemboli from these areas. In cases of hypereosinophilia, eosinophils injure the endocardium and cause the formation of microthrombi on the endocardial surfaces. These microthrombi then embolize to the brain, depositing in the watershed areas.[10] Another possible mechanism includes direct endothelial injury from eosinophil degranulation leading to thrombosis.[11]

Hypereosinophilia is defined as an absolute eosinophil count greater than 1500/μL in the peripheral blood on two examinations that are separated by at least 1 month.[4] Valent et al[4] suggested that hypereosinophilia may also be diagnosed based on histologic examination of tissue when bone marrow biopsy shows greater than 20% eosinophils and/or there is extensive tissue infiltration by eosinophils, and/or specific stain indicates the presence of eosinophil granule proteins. Most common causes of hypereosinophilia are atopic disease and helminth infection.[12] Other less commonly identified causes include myeloproliferative neoplasms, T-cell deregulation, and genetic mutations. In some rare cases, as was suspected in our patient, hypereosinophilia is paraneoplastic[11,13] and is caused by underlying malignant tumors. It is postulated that tumors secrete growth factors which induce leukocytosis and eosinophilia.[13]

A rare neurologic manifestation of HES is inflammatory pseudotumor.[8,14] Battineni et al[8] described a patient with hypereosinophilic syndrome who developed a left cavernous sinus mass, histologic evaluation of which showed fat necrosis, scattered eosinophils, and plasma cell infiltrates. The patient was treated successfully with steroids and imatinib.[8]

Author contributions

Conceptualization, M.T., B.T. and G.H; Writing – original draft preparation, B.T.; Review and editing, M.T. and G.H.; Supervision, G.H. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosure

None to report

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