

# Central Diabetes Insipidus as an Early Presentation of Erdheim–Chester Disease

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Central diabetes insipidus (CDI) is a rare hypothalamus–pituitary idiopathic autoimmune disease caused by a deficiency of arginine vasopressin (AVP) synthesis. Infrequently, infiltrative diseases such as Langerhans cell histiocytosis, immunoglobulin G4-related systemic syndrome, sarcoidosis, and granulomatosis with polyangiitis (GPA) are associated with development of CDI.

Erdheim–Chester disease is a rare form of non-Langerhans cell histiocytosis. This disorder involves the long bones mainly by forming osteosclerotic lesions containing histiocytes. However, multiple organs and tissues are frequently affected, which leads to potentially life-threatening complications. CDI is one of the hallmarks of central nervous system (CNS) involvement and can precede systemic disease by many years.

We present a patient with slowly evolving Erdheim–Chester disease beginning with CNS manifestations, including CDI and central hypogonadism, 6 years before the development of multisystem disease.

## PATIENT DESCRIPTION

We present a 32 year old male patient from our endocrinology clinic. He had been referred to us after complaining of polyuria and polydipsia when he was 24 years old. A water deprivation test showed low urine osmolality 64 mOsm/kg, which increased

to 558 mOsm/kg after a subcutaneous desmopressin injection. A workup of anterior pituitary hormones was normal. Treatment with intranasal minirin 10 µg twice daily was started with a marked improvement in symptoms. Magnetic resonance imaging (MRI) performed in June 2008 disclosed a lack of a posterior pituitary bright spot and the diagnosis of CDI was made.

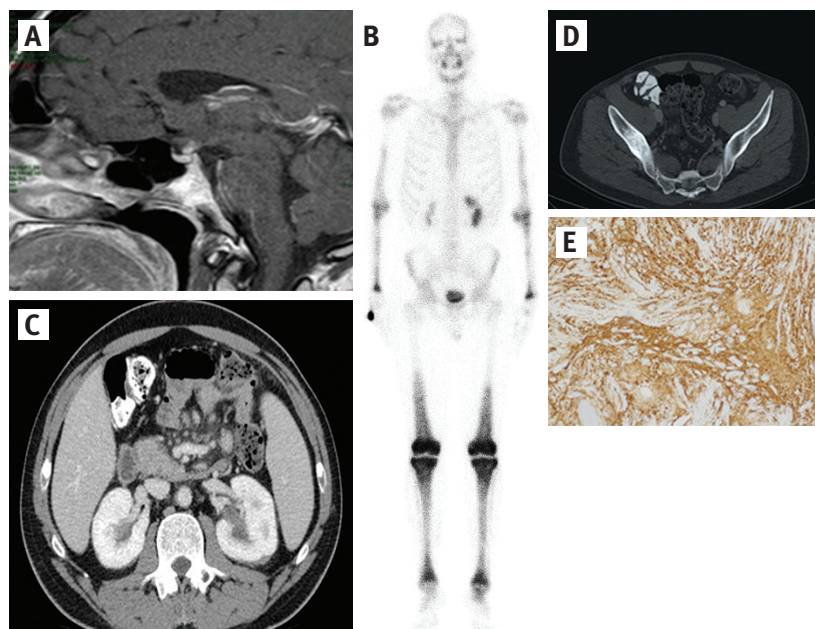
In 2010, the patient began to complain of a lack of libido and a reduced number of morning erections. A new laboratory assessment was performed and he was found to have very low levels of testosterone, luteinizing hormone, and follicle-stimulating hormone. A gonadotropin-releasing hormone test confirmed secondary hypogonadism.

An adrenocorticotrophic hormone test was normal, excluding secondary adrenal insufficiency. Insulin-like growth factor-1, free thyroxine, and prolactin levels were normal. Testosterone replacement therapy was started with an improvement in symptoms of hypogonadism. Another MRI was performed and disclosed a thickened nodular pituitary stalk with a 6 × 6 × 6 mm elliptical lesion, which had not been seen in the baseline MRI [Figure 1A].

After consultation with a neurosurgeon we decided to follow the patient without intervention. To exclude sarcoidosis and other systemic disease, a computed tomography (CT) scan of the chest and abdomen was performed. Nothing abnormal was found.

**Figure 1.** Histopathologic and radiographic findings of patient with Erdheim–Chester disease.

[A] Absent of bright spot, thickened pituitary stalk, [B] Bone scintigraphy with increased uptake in the knees and elbows, [C] Left hydronephrosis with fatty inflammation of mesenteric lymph nodes, [D] Sclerotic lesion of the right iliac bone, [E] Immunohistochemical staining showing marked CD68 positivity



Because of repeated elevated levels of serum alpha-fetoprotein (AFP) (13 ng/ml, normal up to 7 ng/ml), lumbar puncture was performed to exclude a CNS malignancy.

Cerebral fluid analysis disclosed normal AFP and human chorionic gonadotropin levels. In 2014, the patient presented with pain in his ankles and knees. To exclude stress fractures, a bone scan was performed and intense symmetric uptake was found in the elbows and lower extremities [Figure 1B]. The patient was referred to a hematologist because of the suspicion of hematologic disease.

A bone marrow biopsy was performed in June 2014 and revealed 80% cellularity, absence of granuloma formation. Monoclonality was not present in the specimen. In May 2015, the patient was examined by a rheumatologist. A bone densitometry (DEXA) scan was performed, and a low Z score was found in the lumbar spine. He started treatment with alendronate and vitamin D.

Since 2014, his prolactin levels have been elevated and cabergoline treatment was initiated. In December 2015, the patient was hospitalized for severe abdominal pain in the right flank. The abdominal CT scan showed fatty inflammation of mesenteric lymph nodes and a perinephric space compatible with mesenteric panniculitis [Figure 1C]. A new osteosclerotic lesion was found in the right iliac bone on the CT scan [Figure 1D].

In January 2016, he was admitted to the surgery department of another hospital where he underwent explorative laparoscopy, and a biopsy was taken from the omentum. In February 2016 he was admitted to the tertiary hospital for investigation because of severe ankle pain. A bone scan revealed intensive homogenous uptake in the limbs.

A presumptive diagnosis of Erdheim–Chester disease was made and a bone marrow biopsy was taken from the left tibia. A repeat omentum biopsy was performed. Histopathologic examination revealed foamy lipid-laden, non-Langerhans-cell histiocytes CD68 positive, CD1 negative, and S100 negative histiocytes surrounded by medullary fibrosis [Figure 1D]. BRAF V600E mutation was not found.

A recent MRI of the brain performed in December 2016 disclosed the same stalk

lesion and new cerebellar lesions without post contrast axial T1WI enhancement. Cardiac MRI was performed and did not reveal cardiac involvement. Treatment with interferon A was started with a slight improvement in his symptoms

## COMMENT

Our patient presented with apparently idiopathic diabetes insipidus (DI). It is notable that the finding of a thickened nodular pituitary stalk on the MRI, along with the development of central hypogonadism and AFP elevation appeared several years before the systemic involvement.

According to the existing data, inflammatory and neoplastic diseases could involve the pituitary stalk, which could cause partial or complete pituitary hormone deficiencies. The most frequent endocrine abnormalities are central hypogonadism and CDI, which develop in about 30% of cases [1]. Among the inflammatory diseases with a finding of pituitary stalk abnormality, Erdheim–Chester disease was diagnosed in 10% of patients [1].

In another study [2], a thickening of the pituitary stalk in MRI was found in only 15% of patients with idiopathic CDI but in 67% of patients with granulomatous diseases. Interestingly, in that study by Pivonello and colleagues [2], two thirds of patients with histiocytosis X and none with sarcoidosis presenting with DI and thickened pituitary stalk had autoantibodies to AVP-secreting cells, supporting an autoimmune characteristic of this disorder [2]. To the best of our knowledge, there has been no data about the presence of autoantibodies in AVP-secreting cells in Erdheim–Chester disease.

Progressive involvement of the CNS is found in about 50% of patients with Erdheim–Chester disease and potentially can lead to severe functional impairment and death [3]. In our patient, the first manifestation of CNS involvement was CDI, followed by central hypogonadism, hyperprolactinemia and recently new micro-nodular masses in the dentate area of the cerebellum.

The interesting finding in our patient was AFP elevation on several occasions.

He underwent lumbar puncture to exclude CNS malignancy, and normal levels of AFP in cerebrospinal fluid were found. Indeed, lumbar puncture is not recommended in Erdheim–Chester disease since histiocytes do not typically appear in lumbar fluid [3].

As of the acceptance of our research, the patient is not presenting with the symptoms of CNS involvement and his hormonal deficiencies are well controlled. The symptom that continues to bother him is the severe bone pain, which is insufficiently controlled with opioid analgesics.

It is noteworthy that a BRAF V600 E mutation was not detected in the bone marrow biopsy specimen in our patient, which could preclude treatment with tyrosine kinase inhibitors in the future. According to the contemporary guidelines for Erdheim–Chester disease management, it is strongly advised to confirm negative BRAF V600E testing [4] due to its importance for clinical decision making.

## CONCLUSIONS

We presented a case of Erdheim–Chester disease in a patient who was thought initially to have only CDI. In our opinion, isolated CDI with an enlargement of the pituitary stalk should alert the endocrinologists to look for systemic disease.

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