

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version, at <http://dx.doi.org/10.1016/j.jocn.2012.06.016>.

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Superficial siderosis of the central nervous system due to chronic hemorrhage from a giant invasive prolactinoma

Jacob Steinberg^a, José E. Cohen^{a,b}, John M. Gomori^b, Shifra Fraifeld^{a,b}, Samuel Moscovici^a, Guy Rosenthal^{a,c}, Yigal Shoshan^a, Eyal Itshayek^{a,*}

^aDepartment of Neurosurgery, Hadassah–Hebrew University Medical Center, P.O. Box 12000, Jerusalem 91120, Israel

^bDepartment of Radiology, Hadassah–Hebrew University Medical Center, Jerusalem, Israel

^cDepartment of Neurosurgery, San Francisco General Hospital, University of California at San Francisco (UCSF), San Francisco, CA, USA

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ABSTRACT

Superficial siderosis of the central nervous system (CNS) is a rare disorder caused by deposition of hemosiderin in neuronal tissue in the subpial layer of the CNS due to slow subarachnoid or intraventricular hemorrhage. The most common neurologic manifestations include progressive gait ataxia, sensorineural hearing loss, and corticospinal tract signs. We present a case of superficial siderosis in a 43-year-old man who presented to the Emergency Department with sudden onset bilateral visual deterioration and a loss of consciousness. A hemorrhagic giant prolactinoma was diagnosed based on brain CT scan, T1-weighted MRI, and an endocrine blood examination. Susceptibility-weighted non-contrast MRI showed pathognomonic signs of superficial siderosis in the form of a hypointensity rim surrounding the brainstem, cerebellar fissures, and cranial nerves VII and VIII. This report demonstrates that superficial siderosis can be caused by pituitary apoplexy.

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1. Introduction

Superficial siderosis of the central nervous system (CNS) is caused by chronic or repeated bleeding into the subarachnoid space, resulting in hemosiderin deposition in the subpial layers of the brain and spinal cord, and associated parenchymal damage. It is characterized by sensorineural deafness, cerebellar ataxia, and pyramidal signs, and may be associated with dementia, bladder disturbance, anosmia, aniscoria, and sensory signs.^{1–5} In spite of a thorough clinical and imaging assessment, the source of bleeding remains unidentified in a significant proportion of patients.^{2,4}

We present a case of superficial siderosis due to pituitary apoplexy in a patient with prolactinoma.

2. Case report

A 43-year-old man presented to the Emergency Department with loss of consciousness. One week earlier he had experienced sudden onset bilateral visual deterioration, more pronounced in the right eye, and 3 weeks earlier, he had experienced an amnesiac event. He had a history of type II diabetes mellitus, hypertension, and dyslipidemia.

Neuro-ophthalmological examination revealed bitemporal hemianopsia, relative afferent pupillary defect, and optic disc pallor. Visual field examination showed right eye blindness with left temporal hemianopsia.

CT brain scan without contrast showed a large space-occupying lesion involving the sella and sphenoidal sinus, and lytic bone adjacent to the clivus and sphenoid region. The lesion had a hyperdense zone, consistent with calcification, and a hypodense zone that could be interpreted as a cystic component.

* Corresponding author. Tel.: +972 2 677 7092; fax: +972 2 643 1740.

E-mail address: eyal.itshayek@gmail.com (E. Itshayek).



Fig. 1. Sagittal T1-weighted MRI in a 48-year-old male shows a large invasive prolactinoma with a superior cyst invaginating into the third ventricle. Note the hypointense hemorrhagic components in the tumor and cyst.

MRI revealed a giant pituitary adenoma apoplexy compressing the chiasm. A hypointense rim surrounding the brainstem and lining the cerebellar folia was seen on susceptibility-weighted MRI, suggestive of hemosiderin deposits (Figs. 1 and 2). This finding was pathognomonic for superficial siderosis.

His endocrine profile showed a prolactin level of 200,000 MU/L. Other hormonal levels were normal.

In view of recent deterioration in visual function, we offered a surgical procedure to relieve compression of the chiasm. The patient, a single parent who had recently immigrated to Israel from Ethiopia, declined surgery. He was eventually discharged with cabergoline treatment. At 6-month follow-up in Endocrinology Outpatient Clinic, his prolactin level had decreased with cabergoline to 6634 MU/L. Repeat MRI showed a marked reduction in the size of the adenoma and a necrotic zone in the pituitary gland.

3. Discussion

We present a 43-year-old male patient with superficial siderosis due to hemorrhage associated with a giant pituitary

adenoma. To our knowledge, this is the first report of superficial siderosis of the CNS associated with pituitary apoplexy. Chronic hemorrhage preceding the acute apoplexy probably caused the visual and consciousness changes. One patient in the Japanese literature had superficial siderosis of the CNS secondary to prolactinoma.⁶

Superficial siderosis of the CNS was first described in 1908 by Hamill.⁷ In a review of cases published prior to 1995, Fearnley et al.² found dural lesions such as meningocele, pseudomeningocele, cavities remaining after hemispherectomy, chronic suboccipital hematoma, or root pathology such as root avulsions or epidural cysts as frequent underlying pathology. Tumors and vascular abnormalities (arteriovenous malformation, aneurysm) were also seen. More recently, Kumar et al.⁴ reported prior trauma as a possible etiology in 15 of 22 patients with known medical history. Earlier intradural surgery was an additional risk factor in their series. A fluid-filled collection was found in the spinal canal in 14 patients, suggestive of meningocele or pseudomeningocele.

Pituitary apoplexy is defined as a sudden neurological impairment, usually due to a vascular process. The impairment may present with sudden onset headache, visual symptoms, altered mental status, and hormonal dysfunction secondary to acute hemorrhage or infarction in the pituitary gland. Typically a pituitary adenoma is present.⁸

Our patient presented with symptoms of pituitary apoplexy, including recent, sudden-onset deterioration in visual function and loss of consciousness. Brain CT scan showed a large space-occupying lesion of the sellar region. Non-contrast T1-weighted MRI revealed a large invasive prolactinoma with superior cyst invaginating into the third ventricle. The cyst contained a relatively acute hemorrhagic focus (Fig. 1). Hypointense rims surrounding the brainstem, within the cerebellar folia, and surrounding cranial nerves VII and VIII were seen on susceptibility-weighted MRI (Fig. 2), leading to the diagnosis of hemosiderin deposition. This is most likely due to chronic low grade, non-apoplectic, subarachnoid hemorrhage from this giant prolactinoma.

The patient's neurological deficit was attributable to the direct pressure of the tumor on the optic chiasm. The finding of superficial siderosis on MRI mandates an aggressive therapeutic approach to prevent future neurological deterioration. Our patient elected conservative therapy and his giant prolactinoma responded to medical therapy with a marked decrease in size.

Cerebrospinal fluid (CSF) was not tested in this patient; however, CSF analysis typically reveals xanthochromia and an elevated

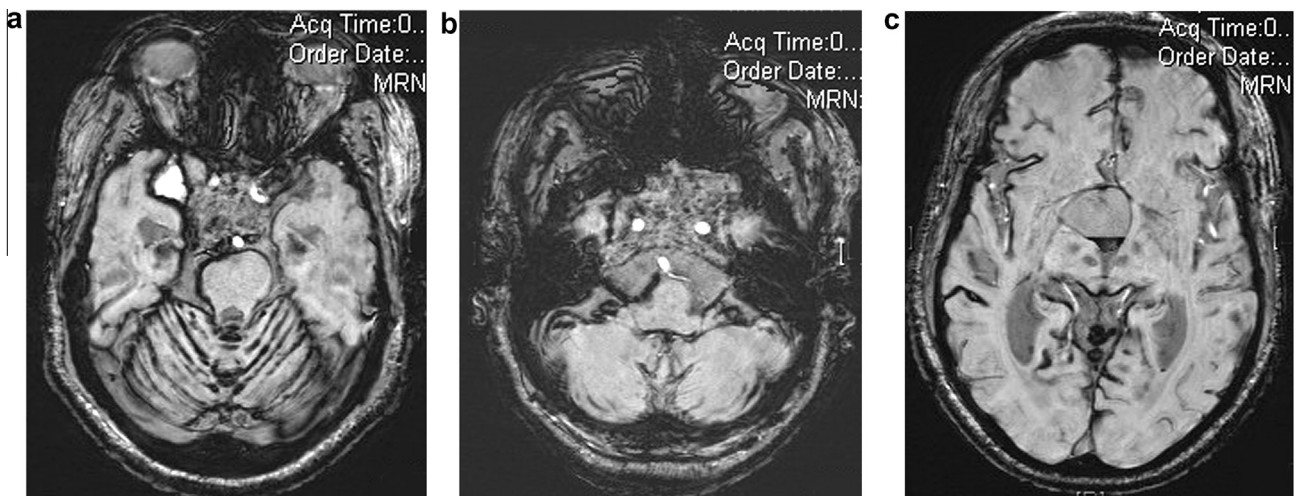


Fig. 2. Axial susceptibility-weighted MRI shows hypointense superficial pial hemosiderin deposits around the brainstem and cerebellar folia, as well cranial nerves 7 and 8, and a superficial cyst with hemorrhagic posterior layering.

red blood cell count in patients with superficial siderosis. White blood cell count and CSF protein may also be elevated; erythrocytes, siderophages, and elevated iron and ferritin levels may or may not be seen, since bleeding is slow and often intermittent. Cerebral and spinal angiography are generally not informative in these patients for the same reason.

Superficial siderosis develops in patients with CSF access to a chronic bleeding source. The brain has the capability of biosynthesizing ferritin for some period by binding iron released by red blood cells. However, when this reserve is exhausted, free radical damage and lipid peroxidation are thought to cause neuronal damage. Patients may experience chronic bleeding for many years before symptoms are manifested. Neurological deficits are irreversible once they develop.³

Slowly progressive cerebral ataxia and sensorineural hearing loss, sometimes accompanied by vestibular failure and/or tinnitus, are typically the first symptoms. Cerebellar dysarthria is also common and nystagmus may be present. Pyramidal and sensory signs relating to brainstem or spinal cord involvement are common. Anosmia and hyposmia are typically not evaluated, but may be present. Optic and trigeminal neuropathy are seen. MRI-pathologic correlation has shown a sharp cutoff in the spinal roots and cranial nerves at the junction between the peripheral Schwann cell and central glial segments.^{1,9} Cranial nerves V, VII, and particularly VIII, have greater vulnerability to hemosiderin deposition due to their longer glial segments. The peripheral nervous system is not involved.

Even a rigorous investigation may not reveal the cause of bleeding in patients with clinical, laboratory, and imaging evidence of superficial siderosis; however, whenever possible, the bleeding source should be identified to arrest progressive hemosiderin deposition, the process of demyelination, and further neurological deterioration. When a source is identified, it should be excised. Re-

peat CSF should show a decrease in xanthochromia and reduced red blood cell levels. Unfortunately, most information regarding superficial siderosis has been gleaned from case reports and small series with relatively short patient follow-up; longer-term assessment is required to better understand the natural history of patients in whom surgical intervention enables successful repair of the bleeding source (as reviewed by Kumar.³)

In conclusion, we describe the diagnosis of superficial siderosis in a 43-year-old man who presented to the Emergency Department with loss of consciousness and sudden bilateral loss of vision. On MRI, a giant invasive prolactinoma with a superior hemorrhagic cyst invaginating into the third ventricle was found. Susceptibility-weighted MRI revealed a hypointense rim surrounding the brainstem, cerebral folio, and cranial nerves, pathognomonic for superficial siderosis.

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Spontaneous cerebellar hemorrhage associated with a novel Notch3 mutation

Sonal Mehta^{a,*}, Prachi Mehndiratta^b, Cathy A. Sila^c

^aSaint Louis University School of Medicine, Department of Neurology and Psychiatry, 1438 South Grand Boulevard, Saint Louis, MO 63104, USA

^bDepartment of Neurology, University Hospitals Case Medical Center, Cleveland, OH, USA

^cDepartment of Neurology, Stroke and Cerebrovascular Center, University Hospitals Case Medical Center, Cleveland, OH, USA

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ABSTRACT

A 55-year-old woman with no significant medical history presented with an acute onset severe headache. A non-enhanced CT scan of the head revealed a right cerebellar hemorrhage. Investigation for etiology of the hemorrhage included an MRI showing extensive subcortical ischemic disease and also several previous microbleeds. The MRI appearance and absence of any other etiology for hemorrhage prompted work up for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). She was found to have a guanosine to thymidine transversion at nucleotide position 1336, codon position 420, resulting in a glycine > cysteine substitution interpreted as “predicted CADASIL-associated mutation”. To our knowledge, this mutation has not yet been reported in association with CADASIL.

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1. Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most common genetic cause of stroke. It is predominantly an ischemic

hereditary arteriopathy caused by a mutation in the Notch3 gene located on chromosome 19p13.1. Notch3 is a 2312 amino acid type I transmembrane protein expressed in vascular smooth muscle cells. The mutations associated with CADASIL affect the exons encoding epidermal growth factor-like repeats, involving loss or gain of cysteine residues. We report a novel NOTCH3 mutation in a patient with spontaneous cerebellar hemorrhage.

* Corresponding author. Tel.: +1 216 235 3497.

E-mail address: dr.sonamehta@gmail.com (S. Mehta).