Focal Pontine Leukoencephalopathy in a Patient with the Shwachman-Diamond Syndrome

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ABSTRACT: A 35-year-old woman who died after a long history of an illness consistent with Shwachman-Diamond Syndrome, was found to have extensive calcified necrotizing lesions confined to the pontocerebellar fibers of the basis pontis. The possible relationship of this recently described lesion to the patient's immunosuppressed state and/or other systemic metabolic disturbances is discussed.

RÉSUMÉ: Leuco-encéphalopathie focale du pont chez un patient atteint du syndrome de Shwachman-Diamond. On a retrouvé des lésions calcifiées nécrosantes extensives limitées aux fibres pontocérébelleuses de la base du pont chez une femme âgée de 35 ans qui est décédée à la suite d'une longue maladie dont l'histoire est compatible avec un syndrome de Shwachman-Diamond. Nous discutons de la relation possible de cette lésion, dont la description est récente, avec l'état d'immunosuppression de la patiente et/ou d'autres désordres métaboliques systémiques.

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Focal pontine leukoencephalopathy (FPL) consists of necrotizing calcified lesions confined to the basis pontis, particularly pontocerebellar fibers therein. The characteristic neuropathology is seen in patients with central nervous system (CNS) involvement by leukemia or lymphoma (in particular after CNS radiotherapy or chemotherapy) and in immunosuppressed patients.[1,2,3,4] This report documents the first occurrence of FPL in a patient with the clinical features of Shwachman-Diamond Syndrome.

Case Report

A 35-year-old white female was diagnosed as having Shwachman-Diamond syndrome, with exocrine pancreatic insufficiency, neutropenia progressing to pancytopenia, and short stature, in the late 1970's. In 1981 she had a normal pregnancy with delivery by caesarean section. Subsequently she was hospitalized multiple times for cellulitis and salivary gland abscesses. She also underwent a left upper lung lobectomy for aspergilloma in January, 1986, five months before death. A bone marrow biopsy (March, 1985) showed essentially aplastic bone marrow. Approximately four months prior to death she was found to have multiple *E. coli* liver abscesses for which she had surgical drainage and was treated with a two month course of intravenous Imipenem. She had been receiving total parenteral nutrition (TPN) because of food intolerance due to the pancreatic insufficiency.

Her final hospital admission was precipitated by shortness of breath and persistent fevers. She also complained of right lateral chest pain which was non-pleuritic in type. She was successfully treated with furosemide for fluid overload. During hospitalization she experienced fluctuations in serum electrolytes, and problems with hyperglycemia (see Table 1) from the TPN, requiring frequent insulin adjustments. Serum sodium levels ranged from 122-146 mmol/L. Plasma glucose level at one point 12 days before death was noted to be 62 mmol/L. At that time she had become confused and disoriented and fell while getting out of bed. The mental status changes resolved with better glucose control and mentation remained essentially normal during the rest of her hospitalization. A computerized tomographic (CT) scan showed a right subarachnoid hemorrhage but no neurologic deficits were noted on examination. She continued to be febrile and had a right pleural effusion. Blood cultures were negative. White blood cell (WBC) counts varied from 300 to 1300 per cu mm (cubic millimeter). A representative WBC differential showed 5% neutrophils, 82% lymphocytes, and 13% monocytes. Prior to death she developed ecchymotic skin lesions and respiratory distress and was given amikacin sulfate and Amphotericin B.

Autopsy revealed a large organized abscess in the right lobe of the liver with extension through the diaphragm into the right lower lobe of lung, replacement of the exocrine pancreas by adipose tissue, hepatomegaly (1825 g) with fatty metamorphosis, and splenomegaly (275 g). Islets of Langerhans were relatively preserved. The brain weighed 975 g (below normal) and showed a 1.5 x 1 cm focus of recent subarachnoid hemorrhage over the right temporal lobe. No lesions were identi-

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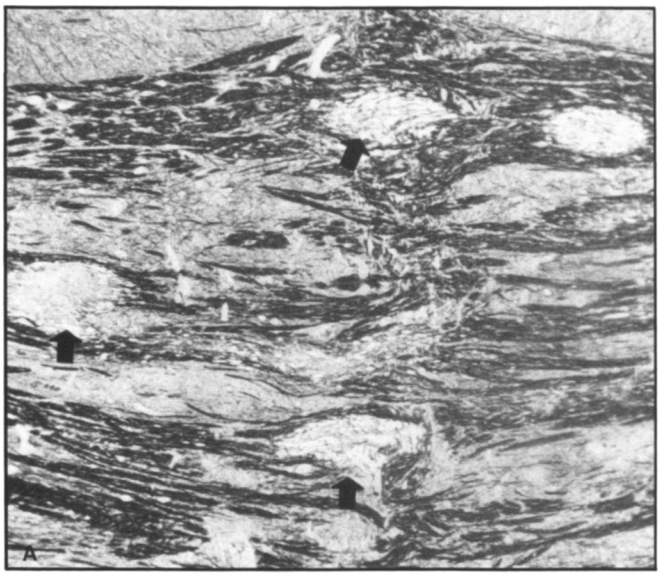
fied grossly in any area of grey or white matter on cut sections after brain fixation in formalin.

Microscopic sections of the pons showed multiple relatively well-demarcated asymmetric lesions within pontocerebellar fibers (Figure 1), with central necrosis, calcification, and numerous neuroaxonal spheroids (Figure 2, 3). White matter adjacent to the lesions showed vacuolization and a negligible inflammatory infiltrate (Figure 2, 3). Pontine nuclei and corticospinal tracts were preserved. No lesions were seen in sections from the remainder of the brain which included medulla, thalamus and cerebral white matter and cortex. The spinal cord was normal.

DISCUSSION

The lesions described in this patient and previously given the name focal pontine leukoencephalopathy (FPL),[4] have been found in a variety of patients: in those who have received chemotherapy and central nervous system (CNS) radiation for assorted malignancies (including a primary cerebellar tumor),[2] in young patients with the primary diagnosis of leukemia or lymphoma,[3] treated by means of systemic chemotherapy (using multiple drugs) and intrathecal medications for meningeal tumor spread, and in a patient with multiple sclerosis who received intrathecal gentamicin sulfate.[5] Similar lesions were induced in normal adult rabbits after intracisternal injection of a much higher dosage of gentamicin and a direct relationship was demonstrated between the cerebrospinal fluid concentrations of the antibiotic and occurrence of the lesions.

Most recently, FPL has been noted in immunosuppressed individuals with acquired immune deficiency syndrome (AIDS)[1] or severe combined immunodeficiency[4] and in a patient with rheumatoid arthritis who may have been immunosuppressed.[6] It has been suggested that compromise of the immune system, accepting the fact that such a term is non-specific, is the common feature in all cases of FPL.[4] The finding of such a lesion in the present patient lends some support to this view, since her leukocyte counts were consistently subnormal and she had a



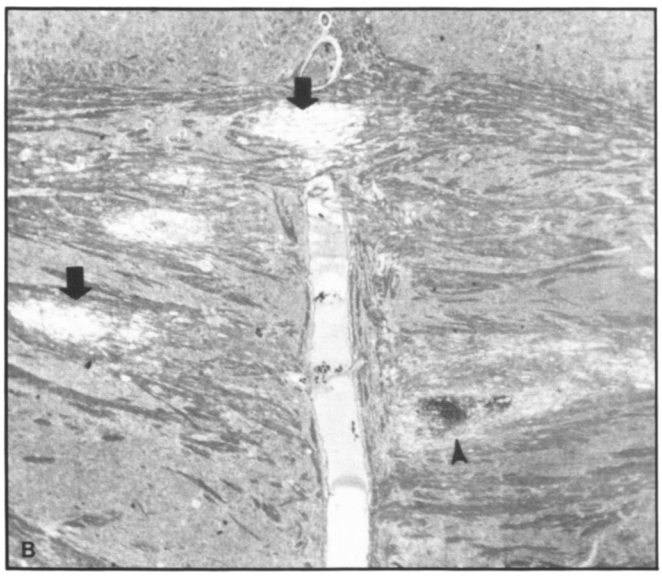
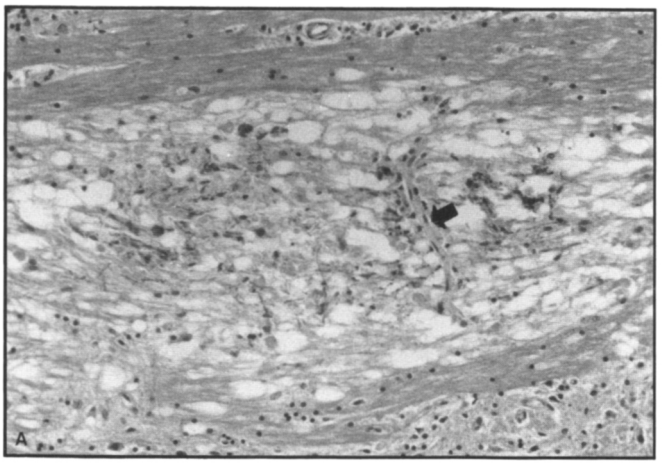


Figure 1 — Low power view of section of basis pontis shows scattered foci of vacuolization within the pontocerebellar fibers (arrows). One lesion (arrowhead in B) shows heavy calcification. Note patent vessel in B. (A Bielschowsky stain, B Weil stain for myelin, both X 23).



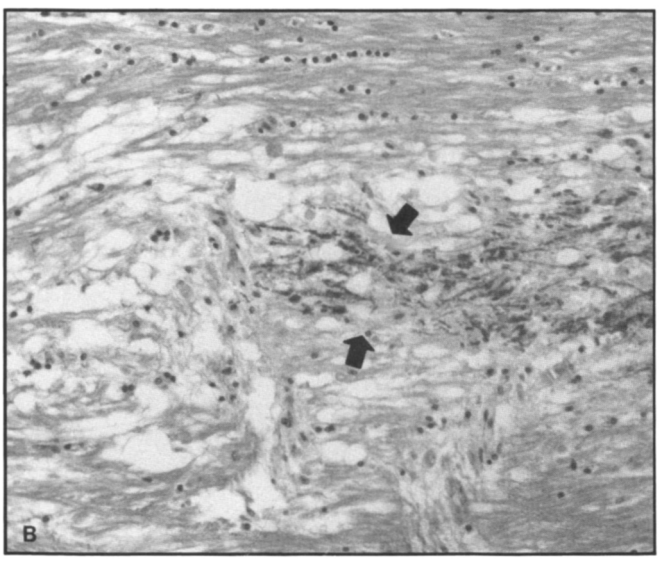


Figure 2 — Details of two foci of leukoencephalopathy with vacuolation and heavily calcified axons (arrows in B). Note normal microvessel (arrow in A). (Hematoxylin and eosin, both X 190).

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long history of infectious complications. Bone marrow dysfunction is an element of the Shwachman-Diamond Syndrome.[7,8] Also of some interest is the fact that she received an aminoglycoside antibiotic during the final admission, though levels of this in the brain or cerebrospinal fluid were not measured.

In view of the frequency of white matter lesions in patients with documented electrolyte abnormalities, and because of the association of another form of pontine pathology — central pontine myelinolysis (CPM) — with rapid correction of hyponatremia,[9,10,11] a detailed review of this patient's glucose and electrolyte levels was undertaken. This showed significant variations in levels of serum Na^+, as well as those of other parameters (Table 1), but no rapid correction of profound hyponatremia of the type associated with, for instance, the osmotic demyelination syndrome or CPM.[12] A single very high blood glucose level was also observed 12 days before death. The consistently abnormal serum calcium and phosphate levels may have contributed to the extent of calcification of the lesions. The contribution of these various metabolic disturbances, or other features of the Shwachman-Diamond Syndrome, to the etiology or severity of the morphologic finding is unknown.

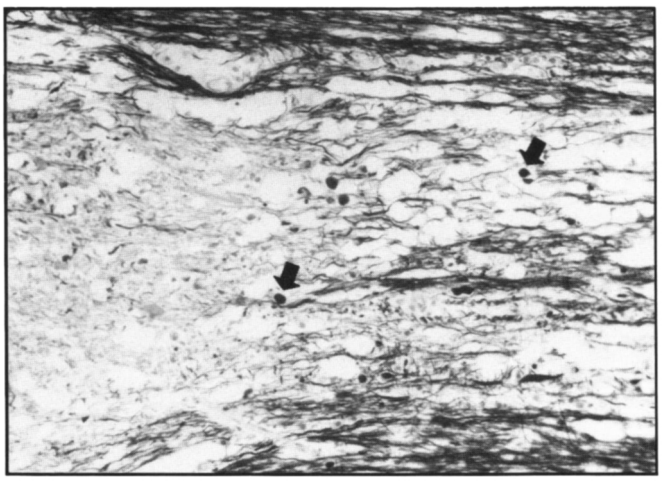

Figure 3 — Prominent neuroaxonal spheroids (arrows) at edge of a focus of FPL (at left). (Bielschowsky stain, X 190).

Table 1: High and Low Values of Biochemical Parameters (all values are serum levels, except glucose, which represents plasma level, and are expressed as mmol/L)

Parameter	Low	Normal Range	High
Na^+	*122* (30)	136-146	146 (12)
K^+	*3.0* (9)	3.6-5.0	*5.4* (53)
Cl^-	*92* (14)	97-110	*119* (12)
Calcium	*1.72* (15)	2.10-2.50	*2.07* (65)
Phosphate	*0.55* (11)	0.84-1.36	*1.61* (0)
Magnesium	*0.55* (15)	0.75-1.05	0.95 (12)
Glucose	5.9 (50)	3.6-6.1	*62* (12)

Italicized values are those outside the normal range.
* Figures in parentheses represent number of days measurement was made before death.

The lesions in this case were restricted to the basis pontis. White matter tracts elsewhere with a comparable morphology (e.g. the internal capsules) were unaffected, though they are involved as part of a more disseminated leukoencephalopathy in other patients with typical FPL.[6] The differences between CPM and FPL have been stressed.[4] However, it is remarkable that both lesions have now been described in separate examples of this rare syndrome.[13] Either this represents a fortuitous occurrence, or one might hypothesize that some component of the Shwachman-Diamond Syndrome predisposes affected patients to develop structural abnormalities in the unique anatomic milieu of the basis pontis. Unfortunately, this case does not assist us in ascribing specific symptomatology to FPL. Careful retrospective clinicopathological analysis (since this is an autopsy diagnosis) of other patients who are found to have FPL will doubtless clarify this issue.

Acknowledgements

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