Leukoencephalopathy Following Combines Therapy of Central Nervous System Leukemia and Lymphoma

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Summary: We report a form of disseminated necrotizing leukoencephalopathy observed in five children with acute lymphoblastic leukemia or lymphoma, who received systemic chemotherapy, brain radiation, and intrathecal (IT) methotrexate, cytosine arabinoside and hydrocortisone because of meningeal tumor involvement. Three children developed a progressive neurologic disease at the end of IT therapy or shortly thereafter. The lesions consisted in discrete, apparently coalescent foci of coagulative necrosis in the white matter, with a remarkable absence of inflammatory cells, little or no tissue breakdown, and striking axonal swellings. The adjacent tissue showed status spongiosus and moderate astrocytic hypertrophy. Vascular lesions were few and inconstant.

Key words: Leukoencephalopathy - CNS leukemia - Intrathecal methotrexate and cytosine arabinoside - Brain radiation

INTRODUCTION

Central nervous system (CNS) involvement in childhood leukemia has been reported to be demonstrable in 50 to 75% of the cases (1). The CNS is also the most frequent site of initial relapse in acute leukemia treated with systemic chemotherapy. As a result, therapy to the CNS, including prophylactic treatment, has been increasingly vigorous in recent years (2, 3). The modes of treatment consist of craniospinal radiation (3), or a combination of whole brain radiation and courses of intrathecal (IT) methotrexate (MT) (2) with or without IT cytosine arabinoside (CA) and hydrocortisone (HC) (4).

Complications following IT chemotherapy in childhood leukemia have included chemical meningitis (5), motor and sensory losses, usually but not invariably (6) transient; and a type of encephalopathy characterized by confusion, somnolence, ataxia, spasticity and major seizures, which may progress to dementia, coma and death (7). Pathologic descriptions of this form of encephalopathy have so far been few (4, 7).

We report the neuropathologic findings of a disseminated type of necrotizing leukoencephalopathy (DNL) whose features are highly distinctive. The patients in our series include four children with acute lymphoblastic leukemia and one child with Burkitt's lymphoma and terminal lymphoblastic leukemia. All were treated with systemic chemotherapy, and with IT MT, CA and HC because of meningeal tumor involvement. Whole brain radiation (in the range of 3,500 R) was given before or during IT therapy. Three children developed, immediately or shortly after completing IT treatment, a neurologic illness characterized by irritability, agitation, confusion, ataxia and slurred speech, progressing to increasing lethargy, decerebrate posture and repeated seizures. Death occurred approximately 2 months after the onset of the encephalopathy.
Fig. 1. Multiple discrete grey foci of softening in cerebral white matter

Fig. 2. Irregular foci of demyelination, with adjacent status spongiosus. Myelin stain, x 30

Fig. 3. Acellular coagulative necrosis (upper right). Reactive astrocytes in adjacent brain. H.-E., x 120