

Hemorrhagic Infarction of the Basal Ganglia

An Unusual Complication of Acute Leukemia

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Abstract. Hemorrhagic infarction of the basal ganglia was observed in 2 young adult patients with acute leukemia who presented with progressive hemiparesis combined with severe mental alterations. In case 1 (AML) lethal infarction due to thrombosis of both internal cerebral veins occurred during induction therapy for relapsed leukemia; in case 2 (cALL) a devastating stroke probably due to deep cerebral venous thrombosis happened during the third remission. Neither of them had hyperleukocytosis, signs of infection, disseminated intravascular coagulation or CNS leukemia. We discuss long-term glucocorticoid therapy (case 1) and combined prophylactic CNS treatment (case 2) as possible risk factors for cerebrovascular thrombosis in acute leukemia.

Introduction

Intracranial hemorrhage and meningeal leukemia are the classical complications of the central nervous system (CNS) in acute leukemia. Prolonged survival in childhood as well as in adult leukemias has produced an altered pattern of complications, most of which have to be considered, at least in part, as side-effects of therapy. This spectrum comprises atypical CNS infections, encephalopathy, cerebral atrophy, intracerebral calcifications, and cerebrovascular complications [1–3]. In this paper we report on 2 young adult patients with acute leukemia who developed unexpected hemorrhagic infarction of the basal ganglia. Infarction occurred late in disease, after extensive antileukemic treatment, but in the absence of CNS leukemia or infection. In the first patient, thrombosis of both internal cerebral veins was found at autopsy. In the second patient unilateral thrombosis of the deep cerebral venous system was assumed on the basis of computerized tomography (CT) in conjunction with clinical data. We consider extended therapy with high-dose glucocorticosteroids (case 1) and intensified

prophylactic CNS treatment (case 2) as possible factors predisposing to cerebrovascular thrombosis in patients with acute leukemia. This unusual, but possibly underestimated complication represents an important differential diagnosis to frank cerebral hemorrhage and leukemic infiltration of the brain.

Case Reports

Patient 1

Figure 1 summarizes the clinical course of this patient. A partial remission was achieved in a 24-year-old woman with relapsed acute myeloblastic leukemia (AML), 10 months after the initial diagnosis. She did well the following 3 months, when she received two cycles of maintenance chemotherapy. 7 weeks after the last cycle she developed severe anemia and rapidly rising peripheral blast counts. She refused readmission and was given red blood cell transfusions and a nonaggressive reinduction therapy consisting of 6-mercaptopurine (6-MP), daily prednisolone (75 mg), and weekly vinorelbine. The blast count fell rapidly within a few days.

3 weeks after initiation of therapy she complained of mild bifrontal headache and vertigo. On admission the following day she was drowsy and disorientated, but responsive to speech. The trigeminal points on the right were tender on pressure. She had a left-side hemiparesis, the leg being more affected than the arm. Babinski's sign was present on the left. She was afebrile, had no

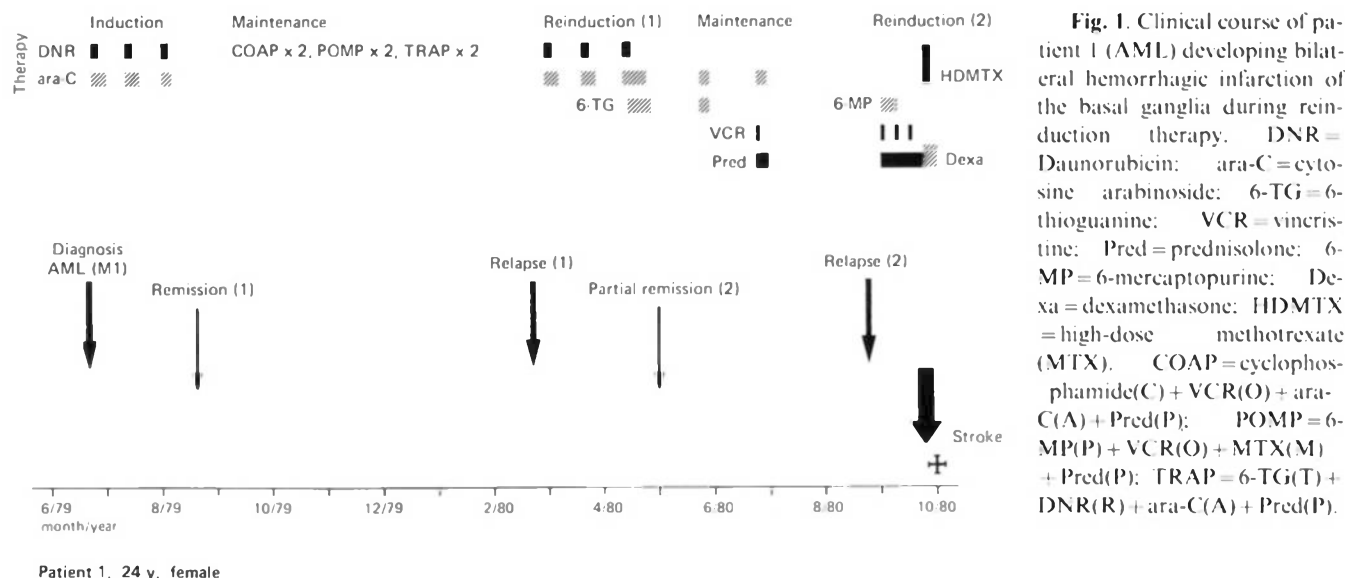


Fig. 1. Clinical course of patient 1 (AML) developing bilateral hemorrhagic infarction of the basal ganglia during reinduction therapy. DNR = Daunorubicin; ara-C = cytosine arabinoside; 6-TG = 6-thioguanine; VCR = vincristine; Pred = prednisolone; 6-MP = 6-mercaptopurine; Dexa = dexamethasone; HDMTX = high-dose methotrexate (MTX). COAP = cyclophosphamide(C) + VCR(O) + ara-C(A) + Pred(P); POMP = 6-MP(P) + VCR(O) + MTX(M) + Pred(P); TRAP = 6-TG(T) + DNR(R) + ara-C(A) + Pred(P).



Fig. 2. Case 1. CT scan showing small area of increased density (hemorrhage) in the right thalamic region with border of low density (edema).

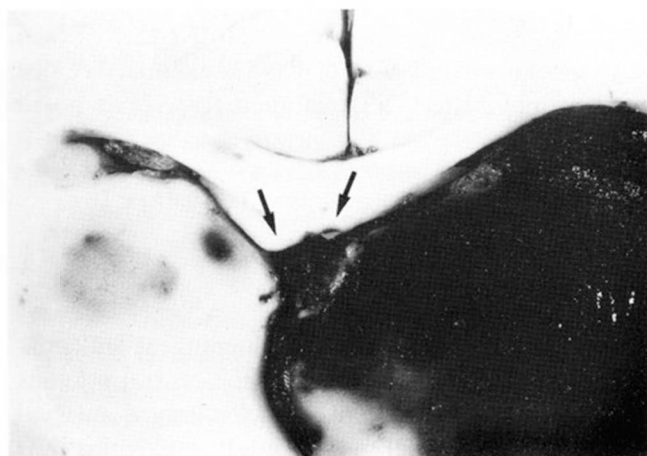


Fig. 3. Case 1. Coronal section of brain at level of thalamus showing thrombosis of both internal cerebral veins (arrows) with extensive hemorrhagic infarction of the right basal ganglia and beginning infarction of the left thalamus.

meningism and no papilledema. Hemoglobin was 9.6 g/dl; leukocyte count was $3.7 \times 10^9/l$ with 45% blasts in the differential smear; platelets numbered $35 \times 10^9/l$. The routine coagulation tests were within normal limits, including a fibrinogen of 2.1 g/l, a prothrombin time of 88% (normal, 75–140%), a partial thromboplastin time of 17.3 s (normal, 17–24 s), and a thrombin time of 12.2 s (normal, 12–16 s). Analysis of single clotting factors revealed an extremely elevated factor VIII activity of 436% (normal, 70–100%). Anti-thrombin III (AT III) was in a low normal range of 76% (normal, 75–130%). No fibrin degradation products (FDP) were identified. She had no signs of bleeding diathesis. Cerebrospinal fluid (CSF) examination was unremarkable. In a CT scan performed immediately after admission nothing abnormal was noted.

Treatment with high-dose methotrexate (3 g m^{-2}) with leucovorin rescue (HDMTX-LV) and dexamethasone (48 mg/day) was started on the assumption of solid leukemic infiltration near the internal capsule. The level of consciousness improved gradually over the following 5 days, but she developed complete left flaccid paralysis. A CT scan 4 days after the stroke demonstrated a small area of increased density with surrounding edema in the right thalamic region (fig. 2). 3 days later she again became drowsy and stuporous. She developed generalized convulsions and lapsed into coma the next day. Antiedematous therapy was without effect. She died 2 days later.

Autopsy of the brain revealed extensive hemorrhagic infarction of the right basal ganglia including the caudate nucleus, internal

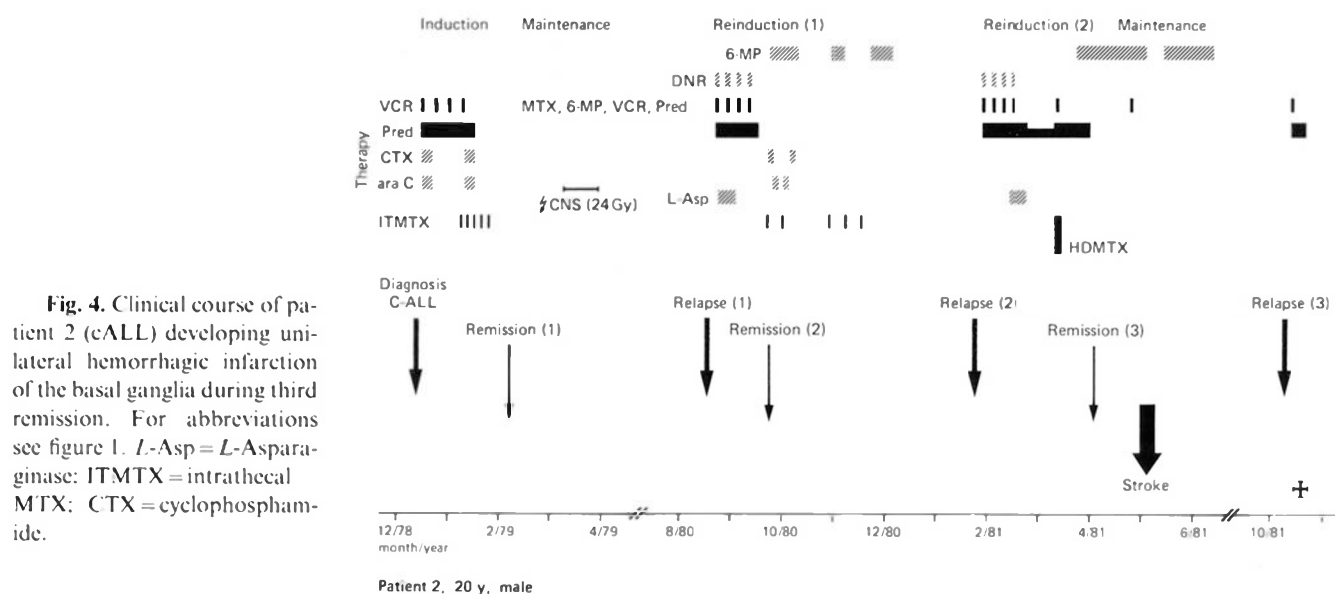


Fig. 4. Clinical course of patient 2 (cALL) developing unilateral hemorrhagic infarction of the basal ganglia during third remission. For abbreviations see figure 1. *L-Asp* = *L*-Asparaginase; ITMTX = intrathecal MTX; CTX = cyclophosphamide.

capsule, putamen, and thalamus and beginning infarction of the medial parts of the left thalamus (fig. 3). Both internal cerebral veins and the vein of Galen harbored recent thrombi. There were no leukemic infiltrates in any of the sections.

Patient 2

The clinical course of this patient is outlined in figure 4. This 20-year-old man with acute lymphoblastic leukemia of common type (cALL) received combined prophylactic CNS treatment after having achieved initial complete remission. After 16 months of maintenance therapy he had his first marrow relapse which was again successfully treated. He was given five further doses of prophylactic intrathecal MTX (ITMTX). After a short remission of 4 months he presented with his second relapse. Reinduction therapy was complicated by severe aplasia and a generalized herpes zoster. It was completed with one course of HDMTX-LV (3 g/m^2) resulting in complete remission.

12 days after resuming maintenance therapy with daily 6-MP the patient awoke one morning with mild headache and some weakness of his right arm. On admission in the evening he had moderate dysarthria, a flaccid right-side hemiparesis chiefly affecting the distal arm, and a mild Horner's syndrome on the left. The right optic disc showed a slight blurring. The peripheral blood values and the coagulation parameters including the AT III level were normal. Cytologic examination of the CSF was negative. The CT scan disclosed discrete zones of hyperdensity in the left basal ganglia region and a small area of low density lateral to the internal capsule (fig. 5a). No focus was seen in the electroencephalogram.

Low-dose heparin and dextran were given for 10 days. During the first postictal week, the hemiparesis deteriorated but remained stable thereafter. The patient showed a rapidly progressive intellectual and emotional decline culminating in lethargy and stupor. These alterations gradually ameliorated within 3 months.

2 weeks after the stroke the CT scan showed a comma-like area of increased density (hemorrhage) laterally to the initial lesions (fig. 5b). This hyperdense area had resolved 3 weeks later, leaving a

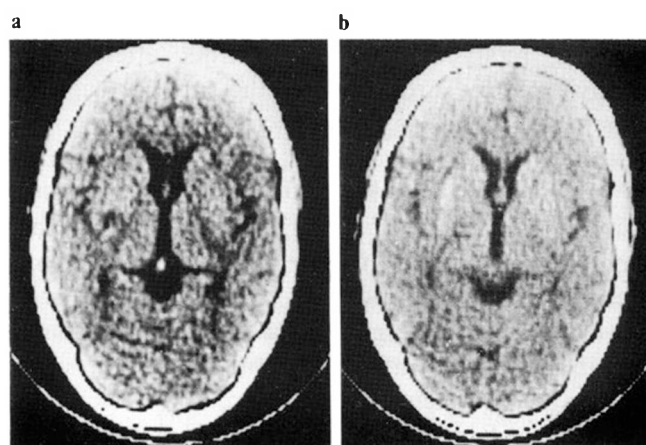


Fig. 5. Case 2. CT scans on day of stroke (a) and after 2 weeks (b). Initial lesions are small zones of hyperdensity in the left basal ganglia region and a small area of low density laterally to the internal capsule. After 2 weeks a narrow area of increased density (hemorrhage) is visible laterally to the initial lesions.

circumscribed area of low density. Thus, retrospectively, a small hemorrhagic infarction of the left basal ganglia was diagnosed. 5 months after the stroke the patient experienced his third marrow relapse. He died of persisting leukemia, without evidence of CNS leukemia. No autopsy was performed.

Discussion

The 2 cases reported have several characteristics in common. Both were young adult patients in an advanced stage of acute leukemia. They presented with

progressive hemiparesis in combination with severe mental alterations. Neither of them had evidence of CNS leukemia, bleeding diathesis or infection. The anatomical site of the lesion was quite similar. Both had *hemorrhagic* infarction of the basal ganglia – unilateral and bilateral, respectively – which was due to thrombosis of the deep cerebral venous system, as proven by autopsy in case 1, and suspected from CT and clinical data in case 2.

In recent years, a small number of cerebrovascular complications in acute leukemia has been reported involving the arterial as well as the venous circulation. Multifocal infarctions of small cerebral vessels have been described in association with generalized infections. Signs of disseminated intravascular coagulation with multiple thrombi in the microvasculature of other organs were detected in these patients [1, 4]. Recently, rare cases of cerebral arterial thrombosis have been observed in children with ALL either during initial induction chemotherapy [5] or during complete remission, several months after CNS prophylaxis [6]. Thrombosis of the superior sagittal sinus in leukemia has been described with leukemic infiltration of the sinus walls [7] and in the absence of any manifest cause [8–10]. In the fatal cases thrombosis had spread within the dural sinus system to the cerebral veins resulting in extensive hemorrhagic infarctions. Isolated thrombosis of the deep cerebral venous (Galenic) system and, in particular, primary thrombosis of both internal cerebral veins with consecutive bilateral hemorrhagic infarction of the basal ganglia (case 1 in this paper) is rare among the spectrum of cerebral venous thromboses [11–13] and has, to our knowledge, not been reported in connection with leukemia.

Primary (aseptic) cerebral venous thrombosis may be met with a variety of disorders including hormonal disturbances [11, 14], various kinds of anemia [12, 15], cardiac disease [16], and chronic wasting disease [9, 16]. The basic pathogenetic factors are attributable to alterations of the vessel wall, viscosity, and hemodynamics. Case 1 showed no evidence of hemodynamic or vascular impairment. Altered viscosity due to leukostasis [17] is very improbable in view of the low peripheral blast count. However, this patient had been treated with high-dose prednisolone for 20 days, when she experienced infarction, and analysis of clotting factors revealed an extensively elevated factor VIII activity (436%). This known side-effect of prolonged glucocorticosteroid therapy [18, 19] may have essen-

tially contributed to the development or aggravation [20] of a hypercoagulable state with consecutive cerebral venous thrombosis. *Priest et al.* [5] postulated that the strokes which they had observed during induction therapy of childhood ALL resulted from depression of AT III and plasminogen levels caused by *L*-asparaginase. Their patients had received prednisolone as well, and in one of them infarction occurred despite a normal AT III value. From our case 1, one may suspect that prolonged treatment with high-dose prednisolone alone may be sufficient in producing cerebrovascular thrombosis in leukemia, possibly by elevating factor VIII levels and/or by interfering with reactive fibrinolysis [21].

In case 2, it cannot be definitely decided from the CT data whether infarction was due to unilateral thrombosis of the deep cerebral venous system or to thrombotic occlusion of penetrating branches of the middle cerebral artery. The hemorrhagic nature of the infarct and the insidious development of symptoms, however, are arguments in favor of venous thrombosis [13, 22]. This patient who had none of the common risk factors of cerebral arterial thrombosis or embolism had received combined prophylactic CNS treatment 2 years before the accident. He was given five further doses of ITMTX and one course of HDMTX-LV, at, respectively, 6 and 2 months before. In recent years, calcifications of the cortex and the basal ganglia have been recognized to be a relatively common late effect of prophylactic CNS treatment in childhood ALL [23]. Perivascular calcifications have been described [24], and MTX is thought to be a main causative factor [25]. The cerebral vessels are possibly also involved in MTX-induced necrotizing encephalopathy, as far as, in addition to the pathognomonic lesions in the white matter, fibrinoid necroses of vessel walls with thromboses and numerous small infarctions have been reported [26]. Based on these literature data, one may speculate that, in patient 2, a preexisting vascular damage in the region of the basal ganglia which was initiated by prophylactic CNS treatment, was deteriorated by additional ITMTX and/or HDMTX-LV and has produced a nidus for thrombus formation. A similar mechanism may have formed the basis of cerebrovascular accidents after CNS prophylaxis in 3 cases of childhood ALL which have been recently reported by *Lalande et al.* [6].

In conclusion, prolonged survival in acute leukemias may result in manifestations of disease not

previously recognized. Among them, cerebrovascular complications of unusual localization may represent an important, possibly underrecognized entity. The exact pathogenesis of deep cerebral venous thrombosis with consecutive hemorrhagic infarction of the basal ganglia in our cases could not be clarified. Further observations are needed to establish a possible connection between certain forms of antileukemic treatment – prolonged application of high-dose corticosteroids and intensified CNS prophylaxis, respectively –, and this type of complication. Deep cerebral venous thrombosis is extremely difficult to diagnose in the absence of early CT changes (case 1!) and may necessitate prompt cerebral angiography. This severe nonblastic CNS complication of acute leukemia should be treatable, of anticoagulants (heparin) are applied before hemorrhagic infarction has developed.

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