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Pediatric acute lymphoblastic leukemia and leukapheresis: CT evidence of hemorrhagic complication

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ABSTRACT

Leukapheresis has been used widely to quickly reduce white blood cell count (WBC) in patients with hyperleukocytosis. Despite its wide utilization, leukapheresis has risks of complication, which have not been thoroughly reported in pediatric patients. No report was found in English literatures about leukapheresis complications in children with acute lymphoblastic leukemia (ALL).

We reported a 4-year-old girl with ALL and hyperleukocytosis, with no sign of bleeding. After leukapheresis, WBC and platelet count decreased, and patient complained of headache. Neurological deficit developed quickly afterwards. Intracranial infection was suspected clinically. Contrast-enhanced head CT revealed multiple hyperdense lesions and diffuse cerebral oedema. The patient was subsequently diagnosed with multiple intraparenchymal hemorrhage, and leukapheresis was stopped.

Intracranial hyperdense lesion in leukemic patients has many differential diagnosis, such as infection, granulocytic sarcoma (chloroma), and hemorrhage. Lesion characteristics in CT could help point the diagnosis. History of leukapheresis should also raise suspicion of hemorrhage. This article discussed CT characteristics of multiple brain hemorrhage in pediatric ALL after leukapheresis and how to differentiate it with other common intracranial complications of leukemia.

1. Introduction

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy, accounting for 25 % of all childhood cancers. Eighty-five percent of childhood ALL are B-cell lineage ALL (B-ALL) [1]. About 5 %–25 % of children with acute leukemia present with hyperleukocytosis at diagnosis. In children with ALL, hyperleukocytosis has been associated with early morbidity and mortality [2–4]. Cerebral haemorrhage can occur as a result of leukocytosis, most commonly in acute leukemia and often leads to death [5]. Leukapheresis has been used widely to quickly reduce white blood cell count (WBC) in patients with hyperleukocytosis, despite unclear clinical benefit for leukemic children [6]. In authors' knowledge, leukapheresis complications in children with ALL have not been reported.

2. Case report

A 4-year-old girl was admitted to Dr Cipto Mangunkusumo General Hospital because of worsening abdominal pain, and later diagnosed with B-ALL.

Her WBC was 6.3 $\times$ 10^5/μL, platelet count was 5.7 $\times$ 10^4/ μL. Prothrombin time (PT) and partial thromboplastin time (aPTT) were normal, and there was no sign of bleeding. Patient underwent leukapheresis to treat hyperleukocytosis.

After the second leukapheresis, WBC decreased to 2.07 $\times$ 10^5 / μL, platelet count was 3.0 $\times$ 10^4 / μL, PT and aPTT were prolonged. Patient complained of headache and neurologic deficit developed quickly afterwards: she had right-sided limb weakness and decreasing consciousness.

Contrast-enhanced head CT was requested with clinical comment "suspected intracranial infection". It revealed multiple intra-axial hyperdense lesions with smooth margins, various sizes in cerebral parenchyma, especially in the left hemisphere, as well as in the midbrain and pons. Density of the lesions were 55–70 HU. Thin perifocal oedema was noted. Diffuse cerebral oedema was also noted (Fig. 1). Patient was diagnosed with multiple intraparenchymal hemorrhage. Leukapheresis

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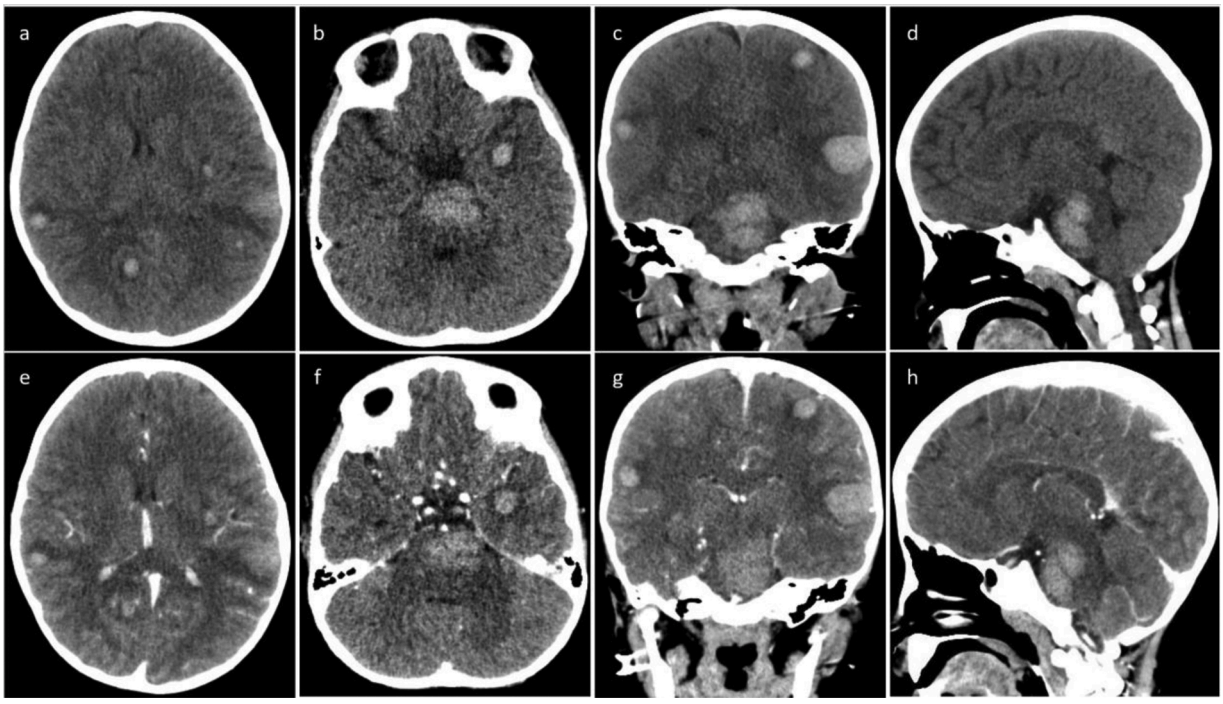

Fig. 1. Non-contrast (**a–d**) and contrast (**e–h**) head CT in axial (**a-b, e-f**), coronal (**c,g**) and sagittal (**d,h**) view showed multiple, non-enhancing hyperdense lesion with smooth margins, various sizes in cerebral parenchyma, especially left cerebral hemisphere, as well as in mid-brain and pons. Thin perifocal oedema was noted. Density of the lesions were 55–70 HU. Diffuse cerebral oedema was present.

was stopped and she was given supportive treatment. Her condition stabilized and 3 weeks later, she was discharged from hospital. She then underwent chemotherapy in the outpatient clinics.

3. Discussion

A hyperdense lesion in leukemic patients could have several differential diagnosis, such as infection, granulocytic sarcoma (chloroma), and hemorrhage. Central nervous system infection is a common complication due to immunosuppression. Toxoplasmosis encephalitis typically appears as multiple hypodense or isodense lesions with surrounding vasogenic edema and mass effect; on contrast it may have rim enhancement [7]. However, toxoplasmosis encephalitis could undergo hemorrhagic transformation and appear on CT as a hyperdense, non-enhancing lesion with mild or no edema in immunosuppressed patients – locations could be in basal ganglia and subcortical in supra- or infra-tentorial. Hyperdense lesions in toxoplasmosis encephalitis could have irregular margins. Hemorrhagic transformation in toxoplasmosis encephalitis usually occurs in human immunodeficiency virus (HIV)--positive patients or leukemic patients following bone marrow transplantation [8]. Fungal infections, such as cerebral aspergillus abscess are not uncommon in leukemic patients; however, it appears as isodense lesions with smooth margin and honeycomb-like clustered rings enhancement on CT [9].

Leukemia could also present as focal leukemic mass in the central nervous system, usually in children with acute myeloid leukemia (AML). It was initially called chloromas, but has been renamed granulocytic (myeloid) sarcomas, and contains primitive myeloblasts, promyelocytes or myelocytes. They typically present as one or more dura-based (extra-axial) iso- or hyperdense masses with strong uniform enhancement on contrast-enhanced CT. Infiltrating, permeative, or destructive lucent lesions in adjacent bones often could be seen on CT. Parenchymal (intra-axial) lesions are much less common than dura-based lesion, they usually present as round, hyperdense lesions with strong and uniform enhancement; hemorrhage could also happen in these lesions [10].

Cerebral metastases could also bleed and appear as multiple hyperdense lesions with perifocal edema on non-contrast CT. Contrast-enhanced CT could show enhancement in the masses. Primary tumors that clasically hemorrhage include lung cancer, breast cancer, melanoma, renal cell carcinoma, choriocarcinoma, and thyroid cancer [11].

In this patient, hyperdense, non-enhancing lesions with smooth margins and its locations involving pons and brain stem did not favor toxoplasmosis encephalitis with hemorrhagic transformation. In acute conditions, cytotoxic oedema favors hemorrhage than infection or malignancy, which usually has finger-like, vasogenic oedema. Lesion density was also consistent with hemorrhage. Moreover, the abrupt clinical symptoms favored intraparenchymal hemorrhage. Leukemic masses or granulocytic sarcomas ("chloromas") could also be ruled out in this patient. First, these masses usually occur in AML, while this patient had ALL. Furthermore, there were no contrast enhancement on the lesions, which favored intraparenchymal hemorrhages than leukemic masses (with or without hemorrhage). This patient also did not have any primary tumor, therefore hemorrhagic metastases could be ruled out. On follow-up, patient's clinical condition was improved by supportive treatment (without chemotherapy, antimicrobial or antifungal treatment), which further showed that the patient actually had multiple intraparencymal hemorrhages.

Leukapheresis have been associated with decreased platelets and fibrinogen, increasing PT and aPTT in both healthy individuals and hyperleukocytic patients – several mechanisms have been suggested, such as procedure-related loss of platelet and blood dilution. While these changes seemed unlikely to cause bleeding in patients with normal coagulation tests, the risk of bleeding complication after leukapheresis remained largely unknown [4].

Louw et al. reported bleeding in 3 % acute myeloblastic leukemic (AML) patients within 24 h after leukapheresis. Bleeding complications in ALL patients after leukapheresis has not been studied yet [4]. Nguyen et al. found that in children with ALL and WBC $\geq 2{,}0 \times 10^5$ /microliter, complications from hyperleukocytosis did not differ between those who received leukapheresis and who did not – indicating the lack of clear clinical benefit for leukapheresis [6].

Leukemia itself could cause disseminated intravascular coagulation,

which result in hypofibrinogenemia and subsequently cerebral hemorrhage. However, cerebral hemorhage in this clinical settings tend to manifest as multiple, small-sized hemorrhages in subcortical white matter [12].

The early morbidity and mortality commonly associated with hyperleukocytosis in children with newly diagnosed ALL might be avoided with conservative management, possibly avoiding the need for costly and potentially dangerous leukapheresis. Adverse effects caused by leukapheresis might even delay initiation of chemotherapy, the definitive treatment for leukemia [8].

In this patient, multiple intraparenchymal hemorrhages especially in the left cerebral hemisphere could be the cause for her right-sided limb weakness. Cerebral oedema, as well as hemorrhages in the mid-brain and pons could be responsible for her decreasing consciousness.

Radiologists should also be aware of the possibility of intracranial hemorrhage in children with acute leukemia after leukapheresis. Collaboration with clinicians is also important to obtain necessary clinical information, and discuss the necessary examination. In this case, contrast CT scan was requested because clinicians suspected intracranial infection. However, radiologists could inform them that non contrast CT revealed hemorrhage only, and a contrast CT was not necessary. This collaboration could have many benefits for the patient, such as decreasing radiation dose and avoiding possible adverse reaction from contrast injection. For the hospital and healthcare services, it could cut unnecessary cost.

4. Conclusion

In children with ALL who underwent leukapheresis, a new onset of neurological deficit should raise the possibility of intracranial hemorrhage. Radiologists should look carefully for the presence of hyperdense lesion in head CT-scan indicating intracranial haemorrhage.

Consent

Written informed consent was obtained from the patient's guardian (parent) of this case report.

Declaration of Competing Interest

The authors have declared that no competing interests exist.

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