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Role of early diagnosis for a noninvasive treatment of pulmonary thromboembolism in leukemic children

Abstract Pulmonary thromboembolism (PTE) in leukemic children undergoing intensive chemotherapy should be promptly recognized so that specific therapy can be started. Our experience with the two cases reported here has led us to propose guidelines for the treatment of initial PTE in a pediatric hematology unit. Two children with leukemia developed PTE, the first during the relapse for acute lymphoblastic leukemia and the second at the onset of acute promyelocytic leukemia. In both cases, the diagnosis of PTE was based on clinical assessment of sudden acute respiratory failure with positive pulmonary perfusional scintigraphy in spite of a negative chest X-ray. The subintensive supervision consisted of instrumental monitoring with the assistance of an intensive care anesthetist. The clinical monitoring was based on the serial registration of respiratory rate, cardiac rate, SaO₂ and body temperature. The thrombolytic therapy, together with heparin prophylaxis, was successfully administered in the hematology ward without the need for

intensive care support (i.e. mechanical ventilation). The success of the treatment was documented by the criterion of a return to the normal cardiorespiratory parameters a few hours after the start of the thrombolytic treatment. Furthermore, a chest CT scan in case 1 and an arteriography in case 2 confirmed the PTE-related hypoperfusion. On the basis of this experience, the authors point out that in the course of acute respiratory failure in leukemic children, the combination of a negative chest X-ray and a positive pulmonary perfusional scintigraphy (compared whenever possible with ventilatory scintigraphy) in the presence of a negative CT scan could be a reliable diagnostic tool for PTE. This pathology should be treated promptly and with specific therapy to avoid progression to a severe, massive PTE.

Key words Children · Leukemia · Chemotherapy · Thromboembolism · Respiratory failure

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Introduction

Acute pulmonary complications are often observed in leukemic children. Most of them are due to infections which could be fatal, reducing the probability of survival [14]. Pulmonary hypoperfusion possibly related to

thromboembolism has rarely been described in children [2, 6]. We have already reported some cases of acute respiratory failure (ARF) [16, 26, 27] due to pulmonary thromboembolism (PTE), which occurred at the onset of leukemia or after bone marrow transplantation (BMT).

Following this experience, we feel it is worthwhile describing two cases of PTE; being diagnosed early, they involved pulmonary hypoperfusion syndrome without severe ARF. Both cases were treated successfully, without the need for invasive measures such as mechanical ventilation.

Case reports

Case 1

A child of 20 months with acute lymphoblastic leukemia (ALL) underwent multiple drug chemotherapy [5] for a relapse of the disease 4 months after the onset. The presence of intraluminal clots resulted in malfunctioning of the central venous catheter (CVC), and treatment with urokinase (UK) was carried out according to the usual procedures [8]. On the 10th day from the start of the antineoplastic treatment for the relapse, she presented with fever (39°C), tachypnea (respiratory rate at rest 50/min) and an initially non-productive cough. Surveillance cultures from blood, throat and stool were all negative. The coagulation data did not show any significant abnormalities.

The patient's respiratory and cardiac rates and body temperature were periodically monitored (every 30 min) as was arterial hemoglobin saturation in O₂ (SaO₂), which was measured percutaneously at room air by means of a pulse-oximeter. The initial chest X-ray and the chest computerized tomography (CT) carried out later on the same day did not show any infiltrate. Twelve hours after the appearance of tachypnea, tachycardia (160 beats/min) and an initial diminution of the SaO₂ (91%) were observed. As standard imaging was negative, a pulmonary perfusion scintigraphy was carried out, which showed two areas of hypoperfusion. Therapy with UK was then started at a dose of 4,400 U/kg i.v., followed by UK 2,400 U/kg i.v. hourly for 16 h.

Therapy with heparin was then given for 10 days, at a dose of 200 U/kg per day i.v.. The monitoring of the fibrinolysis over the course of the combined treatment with UK and heparin revealed maximum levels of fibrinogen degradation products and d-dimers of 380 and 5000 ng/ml, respectively, 12–18 h from the start of the treatment, with a return to normal values 24–36 h from its completion. Tachypnea progressively reduced until resolution. Tachycardia diminished and the SaO₂ values then returned to normal within 18 h. Fever resolved within 24 h and the child then recovered a good general condition.

Twelve days after, a scintigraphy re-evaluation showed a significant reduction in one of the two areas of hypoperfusion. Six days after the start of the respiratory symptoms, a bone marrow aspiration showed that the leukemia was progressing. Despite intensive treatment for the relapse, the child died 8 months later due to progression of the disease.

Case 2

A 12-year-old child, at the onset of acute promyelocytic leukemia, began induction antineoplastic treatment according to AIEOP protocol [1], consisting of a continuous infusion of cytarabine (200 mg/m² per day for 7 days) and rapid-infusion daunorubicin (45 mg/m² per day on the first 3 treatment days). On the 6th day, a CVC was inserted. Five days after the start of induction treatment, the patient presented with an irritable cough, polypnea (40 breaths/min), and fever (38°C). Coagulation tests were normal. The chest X-ray was negative, and so were the routine cultures of blood, urine and stool. The same day, antibiotic therapy with amikacin

and ceftazidime was started and continued for 10 days. Ten hours after the onset of fever, periodic monitoring of the patient revealed tachycardia (160 beats/min), polypnea (45 breaths/min) and reduced SaO₂ (90%).

A perfusion pulmonary scintigraphy was carried out, which showed nonperfused areas in the right lung, at the superior and midlobe levels. Thrombolytic therapy with UK was administered immediately at a dose of 4,400 U/kg i.v., plus 2,400 U/kg i.v. hourly for 12 h, followed by heparin (200 U/kg per day i.v. for 6 days). During the next 24 h, coagulation abnormalities developed and peaked – APTT 123", PT 30%, fibrinogenemia 300 mg%, XDP 1500 ng/ml – with a return to normal over the next few days. A pulmonary arteriography carried out the day after showed that the nonperfused areas previously observed at scintigraphy were partially reperfused. The next scintigraphy, carried out after 12 days, revealed a complete return to normal.

The patient died 55 months after this episode, of septic shock occurring after a relapse of the disease.

Discussion

In our opinion, in pediatric oncology PTE occurs more frequently than is generally accepted [2, 3, 6, 13, 21, 27, 30]. In particular, we have observed such a complication in 2.9% of 452 patients with leukemia undergoing either chemotherapy or bone marrow transplantation in 8 years of experience at our pediatric oncology unit [27]; most of these cases were successfully treated with UK administered in the intensive care unit.

From the physiopathological point of view, an initial PTE as a local event interferes with the circulation of a limited pulmonary area, compromising its function and causing an increase of the respiratory work to compensate [11]. This brings about a rise in the cardiac and the respiratory rates, with a reduction of the arterial and central venous PCO₂ as well as a reduction in the SaO₂ measured in room air, i.e. without supplying oxygen to the patient.

The etiopathogenesis of PTE in patients affected by malignant diseases is related to several factors, occurring either separately or jointly, such as CVC with fibrin deposits along the lumen [6, 13, 30], coagulation abnormalities resulting from the disease and/or the treatment [3, 17, 18, 21, 30], endothelial damage linked to the use of the maximum tolerable doses of antineoplastic drugs [7, 10, 15, 17], rapid "tumor lysis" [16, 24], congenital prethrombotic states [4, 22], thrombogenicity of the parenteral hyperalimentation [28, 29] and the appearance of micro aggregates from transfusion of platelets [9].

Particular attention must be paid to CVC-related thrombosis such as deep venous thrombosis or PTE. In fact, this occurs when the CVC is not functioning very well, as in our case 1; an endothelial cell injury can also occur as a result of the nature of the chemotherapy administered. Our previous experience indicated that the prognosis in PTE becomes more favorable the earlier the diagnosis is made and therapy with fibrinolytics

started. In fact, as shown by other authors, late diagnosis when there is severe lung embolism invariably leads to adult respiratory distress syndrome (ARDS) and often to the death of the patient [16, 20, 26, 27].

As far as we know, reports concerning UK treatment without resuscitatory maneuvers are scarce. Our two patients presented with tachycardia, tachypnea, initial reduction of SaO₂ and fever. They were studied with a nonhomogeneous diagnostic methodology, because not all of the suitable procedures could be carried out at the right time, i.e., during the 24 h following the ARF episode. In particular, and unlike other cases in our previous experience [27], we were not able to perform an arteriography at the time of the development of ARF.

Therefore, it is our opinion that any evidence of ARF in leukemic children, even in the absence of fever, demands a chest X-ray. If radiological findings are negative, a perfusional pulmonary scintigraphy should be considered at once.

Ventilatory pulmonary scintigraphy is not easy to perform in infants and toddlers owing to inadequate cooperation. However, for older children, who often accept the procedures, comparative ventilatory and perfusion scintigraphy should be performed and could represent the gold standard for diagnosis of PTE.

Alternatively, the pulmonary arteriography, as stated by most authors [12], could be a valid tool for diagnosis of PTE, even if not always available in all general hospitals. Whenever the pulmonary arteriography is not available, we propose applying a different diagnostic approach, such as chest CT scan according to three standard slices [23] (apex, hilar structure, base) plus a sample slice of each hypoperfused area. Lack of opacity in the chest CT, which is more detailed than the

standard chest X-ray, confirms the thromboembolic origin of the perfusional scintigraphy images.

In addition, we must stress that during the chest CT scan multiple densitometric evaluations have to be carried out in Hounsfield units (H.U.), to show the beginnings of a possible involvement of the pulmonary interstitial and parenchymal structures [25]. In fact, since the H.U. values correlate to aerated compartments ranging from -1000 to -500 H.U., whereas those for edematous compartments range from -500 to +100 H.U., these measurements represent a good index for evaluating pulmonary diseases such as ARDS.

A further diagnostic advance might consist in the helical (spiral) chest CT. This refined form of CT, with its faster succession of images, can show areas of hypoperfusion in the pulmonary circulation up to the fourth division of the vascular tree in nonanesthetised patients after peripheral vein infusion of a contrast bolus [19]. Prospective studies will be necessary to determine whether helical CT can be offered as an alternative to comparative ventilatory and perfusion scintigraphy as the primary screening modality for acute thromboembolic disease. Despite all its advantages, helical CT may not replace angiography entirely, but it may modify the use of angiography in many patients.

To conclude, our experience suggests that PTE can be effectively treated at an early stage without invasive procedures. To this end, the combined efforts of the pediatric oncologist and the anesthetist are necessary for monitoring and management of such patients.

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References

- Amadori S, Testi AM, Arico M, et al (1993) Prospective comparative study of bone marrow transplantation and postremission chemotherapy for childhood myelogenous leukemia. *J Clin Oncol* 11:1046-1054
- Andrew M, David M, Adams M, et al (1994) Venous thromboembolic complications (VTE) in children: first analyses of the Canadian Registry of VTE. *Blood* 83:1251-1257
- Barzaghi A, Dell'Orto MG, Rovelli A, et al (1995) Central venous catheter clots: Incidence, clinical significance and catheter care in patients with hematological malignancies. *Pediatr Hematol Oncol* 12:243-250
- Catani L, Gugliotta L, Mattioli-Belmonte M, et al (1993) Hypercoagulability in patients undergoing autologous or allogeneic BMT for hematological malignancies. *Bone Marrow Transplant* 12:253-259
- Conter V, Arico M, Valsecchi MG, et al (1995) Extended intrathecal methotrexate may replace cranial irradiation for prevention of CNS relapse in children with intermediate-risk acute lymphoblastic leukemia treated with Berlin-Frankfurt-Münster-based intensive chemotherapy. *J Clin Oncol* 13:2497-2502
- David M, Andrew M (1993) Venous thromboembolic complications in children. *J Pediatr* 3:337-346
- Doll DC, Ringenbergs QS (1986) Vascular toxicity associated with antineoplastic agents. *J Clin Oncol* 9:1405-1417
- Fraschini G, Jadeja J, Lawson M, et al (1987) Local infusion of urokinase for the lysis of thrombosis associated with permanent central venous catheters in cancer patients. *J Clin Oncol* 5:672-678
- Gosseye S, Obbergh L van, Weynand B, et al (1991) Platelet aggregates in small lung vessels and death during liver transplantation. *Lancet* 338:532-534

10. Hoogendoorn MH, Giles AR, Vegh P, et al (1994) Increased endogenous thrombin generation in children with acute lymphoblastic leukemia: risk of thrombotic complications in l-asparaginase-induced antithrombin III deficiency. *Blood* 83:386-391
11. Hurts n (1994) The heart. Arteries and veins, 8th edn, chap XIII: Pulmonary hypertension and cardiopulmonary disease. McGraw-Hill, New York
12. Kelley MA, Carson JL, Palevsky HI, et al (1991) Diagnosing pulmonary embolism: new facts and strategies. *Ann Intern Med* 114:300-306
13. Leiby SM, Purcell H, De Maria JJ (1989) Pulmonary embolism as a result of Hickman catheter-related thrombosis. *Am J Med* 6:228-231
14. Ljungman P, Greaves CA, Meyers JD (1989) Respiratory virus infection in immunocompromised patients. *Bone Marrow Transplant* 4:35-41
15. Manco-Johnson MJ (1994) Disseminated intravascular coagulation and other hypercoagulable syndromes. *Int J Pediatr Hematol Oncol* 1:1-23
16. Marraro G, Uderzo C, Marchi P, et al (1991) Acute respiratory failure and pulmonary thrombosis in leukemic children. *Cancer* 67:696-702
17. Mehta P (1994) Coagulation and platelet abnormalities in patients with cancer. *Int J Pediatr Hematol Oncol* 1:73-85
18. Mitchell LG, Halton JM, Vegh PA, et al (1994) Effect of disease and chemotherapy on hemostasis in children with acute lymphoid leukemia. *Am J Pediatr Hematol Oncol* 16:120-126
19. Remy-Jardin M, Remy J, Wattime L, et al (1992) Central pulmonary thromboembolism: diagnosis with spiral volumetric CT with the single breath-hold technique. Comparison with pulmonary angiography. *Radiology* 185:381-387
20. Sarnaik AP, Lieh-Lai M (1994) Adult respiratory distress syndrome in children. *Pediatr Clin North Am* 41:337-363
21. Schmidt-Sommerfeld E, Snyder G, Rossi TM, et al (1990) Catheter-related complications in 35 children and adolescents with gastrointestinal disease on home parenteral nutrition. *JPEN* 14:148-151
22. Strikwerd S, Van der Velden L, Swart K, et al (1990) Antithrombin III deficiency as congenital risk factor for venous thrombosis and embolism. *Haematologica (Pavia)* 7:407-410
23. Tagliabue M, Casella TC, Zincone GE, et al (1994) CT and chest radiography in the evaluation of adult respiratory distress syndrome. *Acta Radiol* 35:230-234
24. Tobias JD (1991) Tumor lysis pneumopathy. *Clin Intensive Care* 2:305-308
25. Torresin A, Gattinoni L, Pesenti A, et al (1989) Analisi quantitativa della TC polmonare in soggetti normali e in pazienti con edema polmonare non cardiaco. *Radiol Med* 78:626-631
26. Uderzo C, Marraro G, Riva A, et al (1993) Pulmonary thromboembolism in leukaemic children undergoing bone marrow transplantation. *Bone Marrow Transplant* 11:201-203
27. Uderzo C, Faccini P, Rovelli A, et al (1995) Pulmonary thromboembolism in childhood leukemia: 8-years experience in a pediatric hematology center. *J Clin Oncol* 13:2805-2812
28. Wakefield A, Cohen Z, Rosenthal A, et al (1989) Thrombogenicity of total parenteral nutrition solutions. Effect on induction of monocytic/macrophage procoagulant activity. *Gastroenterology* 97:1210-1219
29. Warrier I (1994) Coagulation abnormalities in patients receiving intravenous hyperalimentation. *Int J Pediatr Hematol Oncol* 1:87-91
30. Williams EC (1990) Catheter-related thrombosis. *Clin Cardiol* 13:34-36