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Bilateral Ocular Exophthalmia – A Case of Atypical Acute Myeloblastic Leukemia in a Child

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Abstract

Introduction: In acute myeloblastic leukaemia (AML) explosive proliferation and accumulation of immature myeloid cell clones take place, replacing the bone marrow, with the possibility of the formation of extramedullary tumour masses composed of myeloid cells. The onset of the disease less frequently consists of symptoms of extramedullary manifestation. **Case presentation**: A Caucasian male child aged three years and 11 months was hospitalized for bilateral exophthalmos and otorrhea, due to an alteration in his general condition. Ocular ultrasound revealed an inhomogeneous thickening of the upper right muscles superior to the eyeball. A complete blood count showed severe anaemia, leucocytosis with neutropenia and thrombocytopenia. A peripheral blood smear evidenced myeloblasts. The result of the cytology of bone marrow confirmed the diagnosis of AML. Following blood product replacements and cytostatic treatment (AML-BFM 2004 HR protocol), the remission of exophthalmos and the correction of haematological parameters were favourable. **Conclusion**: In a child with a sudden onset of exophthalmia and altered general condition, the diagnosis of acute leukaemia should be considered. The importance of performing a peripheral blood smear and bone marrow examination is emphasized so that diagnosis and initiation of treatment are not delayed.

Keywords: bilateral ocular exophthalmos, atypical onset, acute myeloblastic leukaemia, myeloid sarcoma

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Introduction

Acute leukaemia accounts for about 30% of all malignancies in children and is the most common cancer in children, of which myeloblastic leukaemia (AML) accounts for about 15% of cases [1]. Leukemic cells can be stored in any extramedullary place, being a rare manifestation and occurring in approximately 3% of cases [2, 3]. Myeloid sarcoma (MS), also known as extramedullary myeloid tumour or chloroma, is a rare neoplasm characterized by the appearance of one or more tumour masses composed of immature myeloid cells in extramedullary sites.

The new World Health Organization (WHO) classification describes this tumour as an MS [4]. It can occur de-novo, precede or appear simultaneously with any myelodysplastic syndrome, myeloproliferative disorders, or most commonly in AML. They are thought to originate in the bone marrow, after which the cells spread through the Haversian canals to penetrate the sub-periosteum and subsequently form soft tissue masses. This would explain the typical location near bone structures [1]. In 9.3% of cases, it occurs in the orbit, due to active haematopoiesis, causing proptosis in one or both eyes [2].

Case Presentation

A 3-years 11-month-old Caucasian male patient's parent noticed the child had pale skin, a dry cough and rhinorrhoea. He was taken to the "Dr. Gheorghe Marinescu" Municipal Hospital of Târnăveni, Romania, where a paediatrician diagnosed him as having acute bronchitis and anaemia. Clarithromycin suspension (Abbvie S.R.L., Campoverde di Aprilia, Italy) 15 mg/kg/day orally, every twelve hours, was prescribed for

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seven days, together with betamethasone/tetryzoline nasal spray (Thea Farma, Settimo Milanese, Italy).

One week after admission to the above hospital, the patient became adynamic, suddenly presenting with proptosis of the right eye (RE). He was seen by the same paediatrician, who, on suspicion of a palpebral tumour and proptosis of the RE, referred him to Mures County Clinical Hospital, Targu Mures, Romania for an ophthalmological examination and assessment.

On referral day the ophthalmologist at the Ophthalmology Clinic, Mures County Clinical Hospital of Targu Mures, Romania reported that the RE showed exophthalmos, orbital asymmetry, normal photo-pupillary reflex and restricted superolateral ocular motility.

Visual acuity was not measured due to the lack of cooperation from the patient.

Fundus examination of the RE revealed retinal and para-palpebral haemorrhages, para-papillary exudate, well-defined, and normally coloured papilla. Ultrasound examination showed inhomogeneous enlarged upper right muscles superior to the right eyeball. There were no abnormal relations of the left eye. A tentative diagnosis of a suspected orbital tumour was suggested.

The child was then referred to the Neurosurgery Clinic, the County Emergency Clinical Hospital, Targu Mures, Romania.

However, one day before admission to the County Emergency Clinical Hospital, right otorrhea developed suddenly and the patient's family self-referred to the Emergency Department (ED) of County Emergency Clinical Hospital of Targu Mures, Romania. The ED doctors decided that the child be hospitalized in Paediatrics Clinic of the hospital.

On admission to the Paediatrics Clinic, the child was reported to have an inconsequential previous medical history and no significant family history. The child had been exposed to passive smoking in the family home. However, it was reported that the patient's sister had been diagnosed with meningioma within the last four months.

On admission to the ED, it was recorded that the child was in a poor general condition. He was 105 cm tall and weighed 22 kg. He presented with a low-grade fever, bilateral exophthalmos which was more accentuated on the right side, pallor of the skin and mucous membranes. Additionally, there was bilateral palpable laterocervical lymphadenopathy, otorrhea of the right ear without palpable organomegaly. Active bleeding occurred at the puncture site of the peripheral venous approach with the formation of a hematoma (Figure 1). Laboratory tests performed at the ED showed severe anaemia (Hgb: 4.2g/dl, Htc: 13.8%), leucocytosis (32090/mm3), neutropenia (0/mm3) and thrombocytopenia (27000/mm3). A non-contrast-enhanced cranial/cerebral CT (NECT) scan was performed showing severe bilateral lacrimal gland hypertrophy, more expressed on the right side, with associated bilateral exophthalmos. The radiologist also described pansinus mucosal thickening and fluid collections in the middle ear cavities and mastoid cells (Figure 2).

On Day 1 post-admission to the Paediatrics Clinic, routine blood tests were performed; the results are shown in Table 1.

A peripheral blood smear (PBS) revealed 27% myeloblasts. The percentage of myeloperoxidase positive blasts was 74%.

Fig. 1. Proptosis of the right eye in the first 24 hours after admission to the Paediatric Clinic

Table 1. Routine tests results performed on Day 1 post-admission to Paediatrics Clinic

CRP	Fg	ESR	LDH	AST	ALT	Creatinine	Urea
41.66 mg/l	497 mg/dl	93 mm/h	601 U/l	21 U/l	8 U/l	0,69 mg/dl	26,1 mg/dl

CRP: C-reactive protein, Fg: fibrinogen, ESR: erythrocyte sedimentation rate, LDH: lactate dehydrogenase, AST:aspartate aminotransferase, ALT: alanine aminotransferase

Serial blood cultures were performed, all being negative.

Bacteriological examination of otic secretion was positive for Staphylococcus aureus MRSA, Corynebacterium.

Blood replacement therapy was administered on Day 1 post-admission, with 10ml/kg red blood cells given twice, 1unit/10kg pooled platelets, through a filter, together with 15ml/kg fresh frozen plasma, the latter two given once only.

Elective antibiotic treatment was initiated with ceftriaxone (Antibiotice S.A, Iași, Romania) 75mg/kg/day on every twelve hours and amikacin (Zentiva S.A., București, Romania) 15mg/kg/day on every twelve hours, both administered intravenously for three days.

Bone marrow biopsy was performed on Day 3 post-admission to the Paediatrics Clinic.

The bone marrow cytology showed a rich cellularity, infiltrated with 30% myeloblasts. Cell immunophenotyping showed the immunophenotypic appearance of AML, detailed in Table 2.

Taking into consideration all the clinical data, laboratory tests results and as well as the imaging data, the case was diagnosed as AML, the exophthalmos being considered to be an extramedullary manifestation of leukaemia.

During the investigations, on Day 3 of hospitalization, right facial paresis occurred. The child was re-assessed by a neurological consultant, and a contrast-enhanced cranial CT (CECT) was undertaken. The CECT demonstrated fluid collections at the level of pansinus cavities, middle ears and mastoid cells. Diffuse extraocular muscles infiltration was described bilaterally (Figure 3).

On Day 4, following the culture of otic secretion, the following antibiotics were prescribed: vancomycin (Xellia Pharmaceuticals ApS, Copenhagen, Denmark) 40mg/kg/day, every six hours together with ceftriaxone (Antibiotice S.A, Iași, Romania) 75mg/kg/day on every twelve hours, both administered intravenously for 14 days; also amikacin (Zentiva S.A., București, Romania) 15mg/kg/day every twelve hours was continued for eight days.

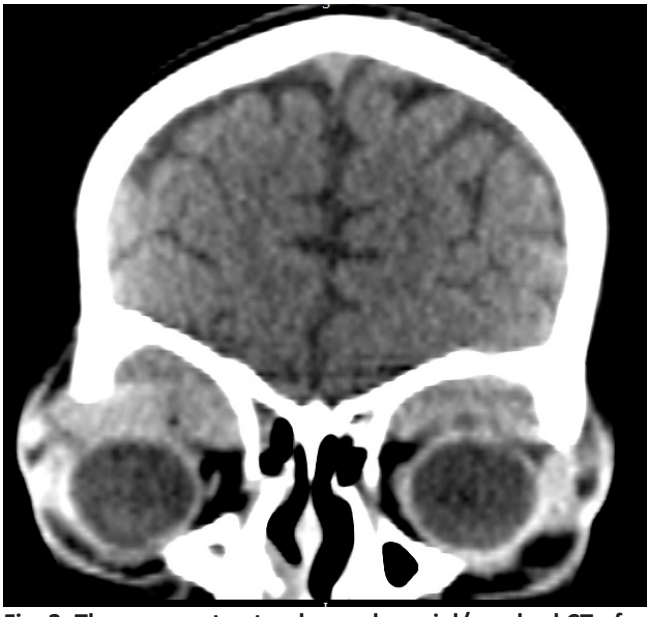

Fig. 2. The non-contrast-enhanced cranial/cerebral CT of the head with coronal sections at the level of the orbits, shows two well-defined, soft-tissue density lesions in the supero-lateral aspect of the extraconal regions bilaterally, more pronounced on the right side, where downward displacement of the ocular globe is visible

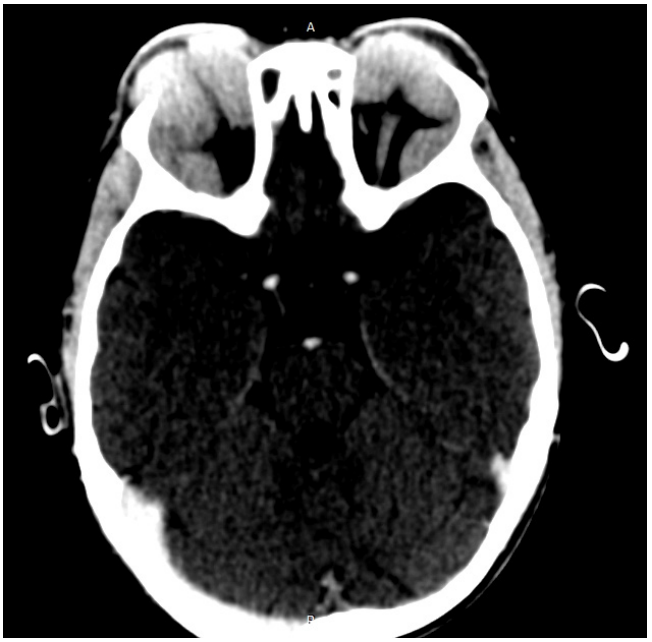

Fig. 3. Contrast-enhanced cranial CT axial view of the head and orbit, following intravenous iodinated contrast media administration. The lesions show mild, homogenous enhancement.

Table 2. Bone marrow immunophenotyping

CD34	HLA-DR	CD13	CD33	CD15	CD117	CD19	CD3	CD7	CD10	CD22	CD11	CD14	CD64
80%	80%	78%	75%	70%	60%	62%	negative	negative	negative	negative	negative	negative	negative

[By flow cytometry; results with aberrant lymphoid line marker (CD19)]

Cytogenetics and molecular features analysis was carried out for risk stratification from blood samples, on Day 4 post-admission. The results were obtained on Day 7.

The FLT3 D835 and DNMT3A R882 mutation was performed by polymerase chain reaction-restriction fragment length polymorphism. For FLT3 ITD and NPM1 fragment analysis was also executed with capillary electrophoresis.

Geneticists did not detect any mutations of examined fragments. Quantitative analysis showed FTL3-ITD:VAR=0% and NPM1:VAR=0.08%.

The heterozygous deletion was shown at the level of the 2p24.3 region (for exons 2, 3 of the MYCN gene), no copy number variants for the other investigated regions was evidenced, and mutation of JAK3 V617F was not detected.

The parents were informed of the oncological diagnosis and the therapeutic regime, after which cytostatic treatment was initiated according to the AML-BFM 2004 HR protocol.

The induction phase, initiated on Day 4 post-admission, consisted of cytarabine (Fresenius Kabi Oncology Plc, Hampshire, UK) 100mg/m^2/day intravenously two consecutive days, followed by 100mg/m^2 over 30 minutes every twelve hours for the next six days, in combination with idarubicin (Actavis Italy S.p.A., Nerviano, Italy) 12mg/m^2/day intravenously on Days 6,8,10 and etoposide (Accord Healthcare Limited, Middlesex, UK) 150 mg/m^2 day intravenously over one hour daily on Days 9-11 post-admission.

At the beginning of the protocol, intrathecal cytarabine had not been administered due to hyperleukocytosis and the presence of peripheral blasts.

On the recommendation of the paediatric neurologist, treatment was initiated with thiamine (vitamin B1) 100mg/2ml (ZENTIVA S.A., Bucureşti, Romania) 50mg with pyridoxine (vitamin B6) 250mg/5ml (ZENTIVA S.A., Bucureşti, Romania) 100mg once a day intravenously. Carbamazepine 100mg/5ml oral suspension (Desitin Arzneimittel GmbH, Hamburg, Germany) was also administered with increasing gradually doses until 2,5ml three times a day.

The chemotherapy regime mentioned above was accompanied by supportive care (Table 3.).

Currently, the patient is undergoing maintenance treatment. Tolerance to cytostatic medication was good, with no significant side effects.

Discussions

In 3% of cases of AML, tumour cells appear in soft tissues, forming myeloid sarcomas [5]. Boys develop MS-associated AML more frequently than girls [3]. MS is associated with AML French-American-British (FAB) subtypes M2, M4 and M5, but may also be associated with other disorders or occur de novo [6, 7]. Ophthalmologic impairment occurs more frequently in patients diagnosed with AML than with acute lymphoblastic leukaemia [8-10]. Bidar et al. (2007) describe the clinical and imaging characteristics of orbital leukemic tumours in pediatric patients. Out of 27 patients, 21 being diagnosed with AML. These chloromas appear as homogeneous masses along the orbital walls, being most commonly encountered in the first decade of life [11]. If the initial manifestation is the orbital tumour, usually within a maximum of one year from the onset of orbital disease, involvement in the peripheral blood and bone marrow occurs [2, 3].

Takhenchangbam et al. (2013) reported the case of a 3-year-old male patient with AML-M3 with extramedullary disease affecting the left eye. The patient had paresis of the left facial nerve and proptosis of the left eye.

Table 3. Supportive care of the induction phase.

Drug name	Strength	Dosage	Route of administration	Dates of administration
human immune globulin (CSL Behring GmbH, Marburg, Germany)	2,5g/25ml	1 fl/day	intravenously	Day 13
red blood cell		10ml/kg	intravenously	Day 9,21
pooled platelets		1unit/10kg	intravenously	Day 7-16, 21-25
trimethoprim-sulfamethoxazole (E.I.P.I.Co., Tenth of Ramadan City, Egypt)	(40mg/200mg)/5ml	2x10ml/day	orally	Day 24-26
fluconazole (Fareva Amboise, Pocé-Sur-Cisse, France)	2mg/ml	100 mg once daily	intravenously	Day 17-27
granisetron (Fresenius Kabi Austria GmbH, Graz, Austria)	1mg/ml	1mg twice a day	Intravenously	Day 4-11

The paresis of the left facial nerve began three months, and the proptosis of the left eye began 20 days before the diagnosis of leukaemia [12].

Young et al. (2016) published a study where they summarized eleven cases of pediatric patients diagnosed with leukaemia and facial paresis. The duration from the onset of facial paralysis to the diagnosis of leukaemia ranged from one day to one month. This association may be explained by a common infection or direct infiltration of the facial nerve with leukemic cells [13].

The present case illustrates the simultaneous diagnosis of orbital tumour and systemic malignancy, with the sudden onset of proptosis with bilateral otomastoiditis and the association of right facial paresis. Difficulties in the diagnosis of the atypical onset of an AML can be avoided by performing a PBS and a bone marrow examination [14-15].

Systemic chemotherapy remains the fundamental element of therapy, in parallel with the replacement of blood products and supportive care. Cranial radiotherapy, as well as hematopoietic stem cell transplantation, remain therapeutic options in selected cases [15-17, 19, 20].

The prognostic implication of MS is unclear. Some studies have shown that patients with AML, associated with orbital MS, have a lower survival rate; however, the results of other studies attest that paediatric patients have significantly better survival than those with isolated AML [15, 17-18].

The presented case has shown a favourable evolution at the time of publishing this report.

Conclusion

The importance is emphasized, of including malignant haematological diseases in the differential diagnosis of child proptosis, in order to diagnose correctly and institute treatment as early as possible.

Informed Consent

Written consent was obtained from the patient's mother for the publication of this case report and any accompanying image.

Conflict of Interests

None to declare.

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