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Clinical Management of Atypical Cases of Acute Myeloid Leukemia Associated with Polyuria-Polydipsia Syndrome

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Abstract: Objectives Acute leukaemia is the most common type of cancer in the paediatric population and the myeloid form represents only 15 percent. In this paper we aim to emphasize the management difficulties of this pathology in pediatric patients. **Prior Work** Studies addressing the costs and burden of acute myeloid laeukemia (AML) in children are sparse in the international literature, due to the low incidence rate, high mortality and some rare clinical aspects, such as polyuria-polydipsia syndrome. Hematologic tests usually can be relevant. Less common complications, that may require urgent intervention, include central nervous system involvement, hyperleukocytosis, and tumor lysis syndrome. There for, the total amount of resources used for the management of these patients represent an important burden for the medical systems all over the world. **Approach** In the current paper we present two clinical cases of paediatric patients diagnosed with AML, associated with leukostasis syndrome, neurologic impairment. **Results**In both cases it was more cost effective to use a rational corroboration of basic diagnostic tools adapted to each clinical form. Due to the fulminant evolution of these patients towards a negative outcome, we focused the most effort and resources on intensive care treatment methods to prolong the survival rate of our patients. **Implications** Such atypical cases may represent a strenuous management challenge for pediatric medical professionals and financial health

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system responsible. **Value** Clinical presenting aspects described in these two cases are extremely rare in pediatrics and represent an effective way to improve medical practice and share a local clinical management experience and resources usage.

Keywords: myeloid; laeukemia; polyuria; polydipsia; management

JEL Classification: I1

1. Introduction

Acute leukaemia is one of the most common types of cancer in the paediatric population, accounting for approximately 30% of all aetiologies. Acute myeloid leukaemia (AML) is a result of malignant transformation of hematopoietic stem or progenitor cells, characterized by loss of differentiation and maturation capacity, representing 15 per cent of childhood leukaemia. Survival rates of AML have greatly improved over the past decades, however, overall survival for children with AML remains lower than cases of acute lymphoblastic leukaemia (Metayer, Dahl, Wiemels & Miller, 2016, S45-S55).

When an AML diagnosis is being suspected, it is necessary to perform an assessment of blast morphology, immunophenotype, cytogenetics, and molecular features (Gamis, Alonzo, Perentesis & Meshinchi, 2013, pp. 964-71).

The peripheral blood smear is a useful investigation tool to evaluate the morphologic aspects of abnormal malignant cells. Myeloblasts are immature cells with large nuclei, prominent nucleoli, and a variable amount of pale blue cytoplasm. One difference between myeloid and lymphoid blasts is represented by the amount of cytoplasm, which is typically more abundant in myeloid cells, associated with the presence of Auer rods or granules (Arber, Orazi & Hasserjian, 2016, pp. 2391-2405). Morphologically the AML has been categorized based upon the French-American-British (FAB) classification that relies on the lineage associated phenotype, ranging from minimally differentiated (FAB M0) to the more mature acute megakaryoblastic leukaemia (AMKL, FAB M7) (Mahmood, Abdullah & Yong, 2014, pp. 3-8).

Another diagnostic tool is the flow cytometry and immunohistochemistry method that can determine the immunophenotype of the tumor cells. Tumoral cells immunophenotype is different between AML and ALL. Although these methods can determine myeloid-specific lineage, the FAB classification is essential, for establishing a final diagnosis. The most common markers expressed in AML are: CD11b, CD34, CD33, CD45, CD64, CD65, CD117, myeloperoxidase (MPO), and lysozyme (Gupta, Pawar & Banerjee, 2019).

In most cases of paediatric AML can be detected different cytogenetic abnormalities, with implications in prognostic and treatment. For detecting this abnormality is used frequently the conventional karyotype. Some translocations can be cryptic, thus is required FISH or DNA sequencing for detection or confirmation. Alongside

conventional karyotyping, fluorescence *in situ* hybridization -FISH should be performed to evaluate for t(8;21), inv(16), t(15;17), and 11q23 translocations (Gulley, Shea & Fedoriw, 2010, pp. 3-16).

AML in paediatric patients present genetically heterogeneity, with different molecular profiles in comparison with adults suffering from AML. Genetic sequencing methods such as polymerase chain reaction-based assays (PCR), and/or next-generation sequencing (NGS), are essential for detecting NPM1, CEBPA, FLT3/ITD, KIT, and WT1 mutations, with implications regarding the prognostic and treatment (Taketani, Taki & Nakamura, 2010, pp. 1975–1977; Alliance, 2009).

Due to the heterogeneous molecular pathogenesis factors, acute myeloid leukaemia is characterized by wide clinical features (Taketani, Taki & Nakamura, 2010, pp. 1975–1977).

The presenting symptoms of AML are directly influenced by the leukemic burden (Blum & Bolwell, 2006, pp. 61-67). These patients can present unspecific symptoms such as fever, malaise, musculoskeletal pains, lymphadenopathy, hepatosplenomegaly, and bleeding. A complete blood count most often reveals anaemia and thrombocytopenia and can have decreased, normal, or increased white blood cell counts with leukemic myeloblasts noted on the peripheral smear.

Another important pathologic element which can be present is disseminated intravascular coagulation (DIC), ranging from mild to severe, especially in some subtypes of AML (eg, acute promyelocytic leukaemia). Symptoms of central nervous system (CNS) involvement such as headache, lethargy, mental status changes, cranial nerve palsies or other extramedullary sites, are less common manifestations at the debut of AML, in children. Significant electrolyte derangements and acute kidney injury and hepatic dysfunction can occur, especially in those with high tumor burden and leukostasis (Masetti, et al., 2015, p. 37).

Furthermore, it has been mentioned in different publications that the hypothalamic - pituitary tract can be infiltrated by leukemic myeloblasts, as well as it can be affected by local thrombosis or bleeding (Wossmann, Borkhardt, Gossen, Gobel & Reiter, 2002, pp. 161-162; Curley, Haughton, Love, McCarthy & Boyd, 2010, pp. 77-79). As a result of these pathological mechanisms, some patients may associate central diabetes insipidus, due to improper vasopressin release or abnormal function of transcription factors, which can be clinically expressed as polyuria-polydipsia syndrome (Harb, et al., 2009, pp. 97-100; Portela & et al., 2012, 516–519). Studies conducted in patients with acute myeloid leukaemia and diabetes insipidus showed an important association with chromosome 7 monosomy and karyotypic changes in 3q21q26 region. Overall, the prognosis is negative, characterised by a poor response to the chemotherapeutic treatment and short survival times (Portela & et al., 2012).

2. Case Reports

Further we present two case reports of acute myeloid leukaemia in paediatric patients and the diagnostic management used.

CASE 1

A case of a 6-month-old female patients admitted into "St Ioan" Paediatric Hospital for skin pallor, petechial skin lesions, mild expiratory dyspnea and fever-38.2 ^{o}C. The onset of symptoms was noticed by the child's mother with 2 days prior the admission. Based on the anamnestic information – there was no significant medical history up to the present episode, as well as no important family medical issues.

Clinical examination on admission revealed- extremely severe general status, intense skin pallor, peripheral oedema and disseminates petechial tegument lesions. Vital parameters- HR-160bpm, O2 saturation- 90%, expiratory dyspnea, hepatic and spleen –megaly, coma- GCS-9pt, no meningeal signs.

Biological investigations – hyperleukocytosis -308.480/mL, severe anaemia-4.4g/dL, Ht- 8.6%, erytropaenia- 700.000/mL, thrombocytopaenia -35.000/mL; high- urea, creatinine and LDH level; metabolic acidosis; electrolyte disturbances, hypoproteinaemia.

Peripheral blood smear revealed blast cells (mielloblast 2%, monoblasts, promonocytes) of variable dimensions, with pale blue cytoplasm, large nucleus without nucleoli and present Auer rods or granules, rare crenelated cells with cytoplasm extensions.

Coagulation parameters: fibrinogen, D-dimer, α-2 antiplasmin, antithrombin, prothrombin time –abnormal values.

Bacteriologic investigations- blood, urine, and CSF cultures – were negative.

Imagistic examinations – evidence of diffuse lymphoblastic pulmonary infiltration.

Based on the anamnestic, clinical, laboratory and imagistic investigations the established diagnosis was acute myeloid leukaemia.

Treatment – the patient received plasma IV infusions, erythrocytes mass, thrombocytes mass, haemostatics, associated with IV fluids, electrolytes, diuretics, pain therapy medication and wide spectrum antibiotics.

Evolution and outcome have been marked by severe prognostic. The infant's state rapidly deteriorated in the first 6 hours after she was hospitalized. Massive haemorrhagic manifestations and severe comatose state (GCS -3pct) were installed, resulted in a respiratory arrest, after which the patient needed to be intubated and ventilated. In spite of aggressive intensive care therapeutic measures, the patient associated acute renal and hepatic failure, as well as severe electrolyte imbalances.

After approximately 18 hours since the admission into the ICU the infant suffered a cardiac arrest on respiratory ventilation support, which was unresponsive to all resuscitations measures included in the advanced life support (ALS) protocol.

CASE 2

A case of 12-year-old male patient, transferred from another medical unit into "St. Ioan" Paediatric Hospital, for acute onset of facial cranial nerve palsy and lethargy. The anamnestic information revealed that the current episode had begun approximately 4 days prior to the hospital admission with myalgia, left lower limb pain with progressive evolution and functional impotence. The adolescent presented in an emergency department where a complete blood cell count was performed and revealed important leucocytosis (130.000/mL), monocytosis-63.5%, anaemia and thrombocytopenia. An emergency cerebral CT scan showed intraventricular haemorrhage. Under these circumstances the patient was transferred to our intensive care unit, for further treatment measures. The patient had no important medical issues in the past, and no hospitalizations. Also, there was no significant medical condition regarding the other family members.

Clinical findings on admission day- altered general status, skin pallor, myalgia, normal conscious state GCS-15pt, no meningeal signs, and stable vital parameters.

Biological investigations on admission revealed – hyperleukocytosis -140.430/mL, anaemia- 6.04g/dL, Ht- 8.6%, erytropaenia- 1.79*10^6/µL, thrombocytopaenia - 11.100/mL; high- urea, creatinine and LDH level; metabolic acidosis; electrolyte disturbances, hypoproteinaemia

Low fibrinogen- 73mg/dL; high - D-dimer level; prothrombin time-16.6s; INR- high, and severe low platelet count.

The peripheral blood smear identified- blast cells- 85% atypical promyelocytes, with large nucleus, visible nucleoli, hypogranular cytoplasm; rare promielocytes with Auer rods.

In this case, the diagnosis was acute promyelocytic leukaemia.

The patient immediately underwent aggressive supportive treatment including – plasma, erythrocytes, and platelets transfusions, as well as coagulation factors IV administration in order to counterpart the coagulation impairment and dysfunction. Other therapeutic lines included antibiotic therapy, IV fluids, electrolyte infusions, mannitol 10%. In spite of all intensive care measures the evolution of this patient was unfavorable- as severe comatose state (GCS 3pct) was installed and he presented severe desaturation periods which needed intubation and mechanical ventilation. The hematologic dysfunctions accentuated, and haemorrhagic syndrome rapidly installed- visible ecchymosis, petechial lesions and active mucosal haemorrhage were present. Clinical polyuria has been associated, as a result, the patient had a urine

output of approx. 55ml/kgc/24h with low density (400 mOsm/kg). Intravascular disseminated coagulopathy appeared associated with renal and hepatic insufficiency and electrolytic derangements worsened the outcome of the patient. In the 5th day from the initial diagnostic – he presented hemodynamic instability and cardiac arrest – which was unresponsive to all resuscitation therapeutic measures.

3. Discussions

Patients affected by acute leukaemia and often present hyperleukocytosis defined as a white blood cell count greater than 100,000/mL, which is associated with increased morbidity and mortality. In paediatric AML, higher WBC counts are more common in patients presenting with FLT3/ITD, MLL rearrangements, FAB M4 and M5 phenotypes. The poor prognosis is due to high early death rate secondary to leukostasis which is a syndrome caused by the sludging of circulating leukemic blasts in the microvasculature (Giammarco, Chiusolo, Piccirillo et al., 2017, pp. 147-154) Furthermore, hyperleukocytosis lead to tissue damage from blast infiltration, resulting in haemorrhagic and thromboembolic events. The clinical presentation of leukostasis varies depending on the affected organs and it is an oncologic emergency. Based on these elements, patients with lung involvement may associate respiratory failure, while neurologic involvement may manifest as somnolence, focal neurologic deficits, or coma (Gong, et al., 2014, pp. 1825-1827). This was the pathologic mechanism in the first clinical case presented. The 6-month-old patient was diagnosed with acute myeloid leukaemia complicated with leukostasis syndrome, due to which the infant succumbed in the first day after diagnosis. Although it is well established the role of complex genetic testing for guiding the further therapeutic management in leukaemic pediatric patients, in this case it was not the best option, due to the fulminant evolution towards a negative outcome. Genetic testing represent one of the most expensive aspects included in the general management of these type of patients, as well as long term specific onco-hematological treatment.

Tumor lysis syndrome (TLS) was present in both cases – In order to counterpart, this complication supportive management should include hyperhydration to reduce risk of tumor lysis and decrease blood viscosity. TLS may manifest as hyperphosphatemia, hypocalcaemia (caused by precipitation of calcium phosphate), hyperuricemia, hyperkalaemia, and acute renal failure. Leukemic cell lysis can cause over-production and over-excretion of uric acid. The precipitation of uric acid in the tubules can lead to oliguric or anuric renal failure known as uric acid nephropathy (Belay, Yirdaw & Enawgaw, 2017). There for, the general management costs are exponentially increased in such patients.

In acute leukaemia patients have a hypercoagulable state and a risk for thrombohemorrhagic complications. Clinical manifestations may range from

localized thrombosis to active haemorrhage of varying degrees of severity. The pathogenic mechanism of these elements is the acute disseminated intravascular coagulation (DIC), which occurs most commonly in patients presenting with hyperleukocytosis, monocytic subtypes (FAB M5), or with acute promyelocytic leukaemia (APL). Supportive care of patients with AML-associated DIC should include standard management with appropriate blood products (eg, platelets and coagulation factors), which is essential to minimize bleeding risk (Barbui & Falanga, 2001, pp. 593-604; Hatzl, Uhl, Hinterramskogler, et al., 2018, pp. 146-151). In spite of using the required medical and financial resources in the second case presented, the patient succumbed after 5 days of hospitalization. The most important amount of the finacial resources have been used especially for intensive care measures and other supportive therapeutic interventions.

4. Conclusions

The main characteristic of acute myeloid leukaemia is a clonal proliferation of myeloid precursors with reduced capacity to differentiate into more mature cellular elements. Furthermore, high disease burden is associated with poor outcomes for patients with acute myeloid leukaemia, and as consequence higher management costs are needed.

The risk of serious complications and mortality from leukemic pathological mechanisms is highest at the time of diagnosis and within the days following the initiation of therapy. It is important to recognize that the WBC count is a somewhat arbitrary threshold and does not always predict the presence of complications but is the most efficient and cost-effective way to obtain a presumptive diagnosis.

It the future management of these type of patients is important to consider the fact that acute myeloid leukaemia may be associated with atypical manifestations such as polyuria-polydipsia syndrome. In the medical literature, it is mentioned that less than 2% of all patients with central diabetes insipidus have as an underlying cause, in fact, the acute myeloid leukaemia, and less than 1% of all AML are associated with polyuria before the diagnostic or it is developed during the leukaemia progression (14). Compared with acute lymphoblastic leukaemia (ALL), complications of hyperleukocytosis are more common and can occur at comparatively lower WBC counts in AML. Atypical clinical form is an important factor for increasing the total costs needed for the medical management of patients suffering from leukemia.

One of the main future perspectives may be represented by the conducting of clinical studies in pediatric patients, in order to develop new diagnostic algorithms, based on the most cost-efficient and medical practices.

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