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A case report of blastic plasmacytoid dendritic cell neoplasm in a hispanic child

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ABSTRACT

Plasmacytoid dendritic cell neoplasms are aggressive and rare hematologic malignancies characterized by clonal expansion of plasmacytoid dendritic cells with frequent cutaneous involvement. The pathogenesis is not well established, and it shows enhanced expression of CD56, CD4 and CD123 detected by flow cytometry and immunohistochemistry. We report a case report of this rare disease in a hispanic child with complete remission after using a protocol for high-risk acute lymphoblastic leukemia.

Abbreviations

BPDCN	Blastic Plasmacytoid Dendritic Cell Neoplasm
INEN	National Institute of Neoplastic Diseases (Lima, Perú)
HR-ALL	High-risk acute lymphoblastic leukemia
ALL	Acute lymphoblastic leukemia

1. Introduction

Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) is a rare hematological neoplasm, which has its own category in the group of leukemias [1]. It has been reported close to 0.04 per 100,000 incidence population worldwide [2], while probably heterogeneously distributed, Latin America's incidence is still unknown.

It usually presents in elderly people, and clinical manifestations include nodular blue-violet skin lesions, bone marrow infiltration and, less frequently, extramedullary involvement [3]. In pediatric patients, clinical characteristics do not differ significantly; however, better survival has been found in children [3, 4]. Despite some associations with other hematologic neoplasms that have been described, its etiology is still not clearly known [5]. Diagnosis is based on immunohistochemistry; it requires the positivity of CD4 and CD56 markers, and at least two other dendritic cell markers [6].

Current literature, based on case reports in children supports the use of acute leukemia treatment regimens as the most beneficial option [7]. While, recently, a larger cohort in adults has reported the best outcomes for AL-like regimen followed by allogenic hematopoietic stem cell transplantation [8]. Although there is no standardized treatment for BPDCN, one study reported that adults treated with AML-like, ALL-like and high-dose methotrexate with asparaginase (Aspa-MTX) chemotherapies showed increased survival and remission compared to other treatments such as CHOP-like (classical regimen used in the treatment of non-Hodgkin lymphomas and combining cyclophosphamide, doxorubicin, vincristine, and prednisone) and not otherwise specified (NOS) regimens (all other drugs alone or in combination) [9]. In pediatric patients, despite lacking standardized treatment, good results have been obtained with new therapies targeting CD123 like SL-401 (tagraxofusp) [10] which are currently approved and used as more specific treatment in adults and only few reports in children, this approach is not yet standardized, but good results have been seen with the pediatric ALL protocol [11] in children and young adults.

The objective of this current pediatric case is to document the diagnosis of this rare disease in a child without any clinical suspicion of leukemia and report complete remission after of an institutional

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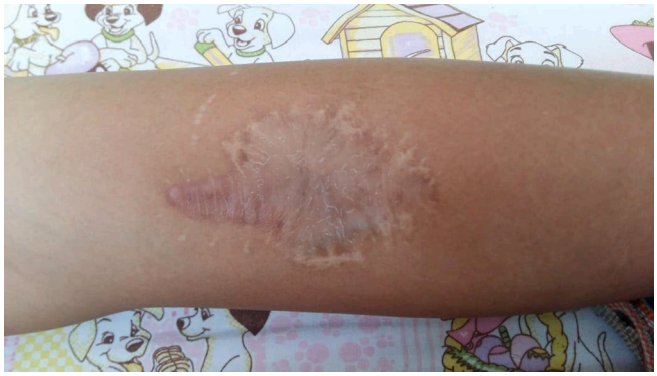

Fig. 1. Lesion appearance after 24 months from diagnosis.

protocol for high-risk acute lymphoblastic leukemia (HR-ALL).

2. Case report

We report a case of an 11 year old male from Peru who was referred from a local hospital in the highlands to the National Institute of Neoplastic Diseases (INEN) in Lima, with the diagnosis of 'Round Cell Neoplasia'.

This child presented with a 2-year clinical history of a growing mass in the anterior inner middle third of the right leg, of approximately 5 cm by time of medical consultation, blue-violet coloring, increased consistency, poorly defined edges and mild pain on palpation, without functional limitation. No other epidemiological, personal, family or medical history of importance was reported.

The physical examination showed a 7 cm long surgical scar with ulcerated area and granulation tissue without signs of infection seen from the past biopsy (Fig. 1). Also, he presented right inguinal multiple adenopathies of 3 × 3 cm, mobile, painless and without phlogosis. The rest of the physical examination was unremarkable.

Final diagnosis was made through immunohistochemistry and by excluding more frequent neoplasms. Thus, the positivity for CD4, but negativity of CD3, served to rule out a T cell neoplasm. In the same way, a positivity for CD56, but negativity for CD3, removed the possibility of T-NK lymphocyte involvement; and negativity for CD34 excluded the presence of myeloid cells [6]. Immunohistochemistry showed CD4+, CD56 +, in addition to 2 positive dendritic cell markers (CD123 and TCL1) which allowed confirmation of the diagnosis [13]. Other dendritic cell markers not tested in this case are CD68, CD123 and BDCA-2/CD303 [14]. This patient also showed positivity for terminal deoxynucleotidyl transferase (TdT), which is associated to a better prognosis [8].

Laboratory values of hemoglobin, leukocytes, segmented, platelets, and erythrocyte sedimentation rate values were normal. Morphology, flow cytometry and bone marrow biopsy were negative to infiltration of neoplasm cells. After the medical team discussion, an institutional HR-ALL treatment protocol, based on the pediatric one from the International BFM Study Group (BFM-95), was indicated (Table 1). The high-risk classification was indicated because of the patient's age and the biological characteristics of this rare disease. Patient had complete response after protocol given with remission currently.

During treatment, two emergent admissions were required due to febrile neutropenia, and both resolved without complications. By the date of submit of this report, the patient was in good general condition. He completed maintenance chemotherapy phase in May 2020, and stays in follow up appointments without treatment related complications.

3. Discussion

Only 74 pediatric cases of BPDCN worldwide were described in a 2017 review [3]. However, it did not include data in Spanish or from Latin America, and its clinical progress has not been considered before. Also, this patient experienced a delay in diagnosis due to lack of resources at a hospital outside the country's capital (as seen in many low-middle income countries), which points out the indolent course of the neoplasm in this case. A systematic literature review showed the mean survival of patients under 40 years was 38 months [3]. Similarly, another study showed the overall survival in children at 3 years was 57.4 ± 10.2 months [15].

Table 1
High-Risk LLA protocol used (modified from BFM-95).

Phases and procedureS		
	Dosis	**Days**
Phase IA		
Dexamethasone(IV/VO)	6 mg/m^2/day	1–29
Prednisone (VO)	60 mg/m^2/day	1–29
Vincristine (IV)	1.5 mg/m^2	1, 8, 15, 22
Daunomycin (IV)	30 mg/m^2	1, 8, 15, 22
L-Asparaginase (IV)	10,000 UI/m^2	3, 6, 10, 13, 17, 20
Lumbar puncture with QTIT application	–	7,14
Bone marrow study	–	7+/−14
BM study with EMR and LP with QTIT application	–	29
IB PHASE increased		
Cyclophosphamide (IV)	1000 mg/m^2	1, 29
Cytarabine (IV)	75 mg/m^2	1–4, 8–11, 29–32,36–39
6-Mercaptopurine (VO)	60 mg/m^2/day	1–14 y 36–49
Vincristine (IV)	1.5 mg/m^2	15, 22, 43, 50
Asparaginase (IV/IM)	10,000 UI/m^2	17, 20, 24, 27, 45, 48, 52, 55
Lumbar puncture with QTIT application	_	14, 28, 42
MO study with EMR and PL with QTIT application	_	At the end of this phase
Consolidation		
Methotrexate (IV)	2 g/m^2	1, 15, 29, 43
Leucovorin(VO)	15 mg/m^2	42, 48 y 54*
Vincristine (IV)	1.5 mg/m^2	1, 15, 29, 43
Mercaptopurine (VO)	25 mg/m^2/dosis	1–56
Lumbar puncture with QTIT application	_	28
MO/PL with QTIT application	_	At the end of this phase
Increased induction (Phase II or increased re-induction)		
Vincristine (IV)	1.5 mg/m^2	1, 8, 15, 22
Doxorubicin (IV)	25 mg/m^2	1, 8, 15, 22
Dexamethasone (VO)	6 mg/m^2	1–21
L-Asparaginase (IM)	10,000 UI/m^2	3, 6, 10, 13
Lumbar puncture with QTIT application	_	14, 35
Cyclophosphamide (IV)	1000 mg/m^2	36
Cytarabine (IV)	75 mg/m^2	36, 37, 38, 39, 43, 44, 45, 46
Thioguanine (VO)	60 mg/m^2/día	36–49
Vincristine (IV)	1.5 mg/m^2	50, 57
Asparaginase (IM)	10,000 UI/m^2	52, 55, 59, 62
Lumbar puncture with QTIT application		42
BM/LP with QTIT application	–	At the end of this phase
Maintenance		
Vincristine (IV)	1.5 mg/m^2	1
Prednisone	40 mg/m^2	During 5 days
Mercaptopurine (VO)	50 mg/ m^2	Daily
Methotrexate (VO)	15 mg/m^2	Weekly
Lumbar puncture with QTIT application	_	Monthly (6 months)

VO: oral; IV: intravenous; IM: intramuscular; QTIT: intrathecal chemotherapy; BM: Bone marrow; LP: Lumbar puncture; EMR: minimal residual disease; *: Hours after initiation of methotrexate.

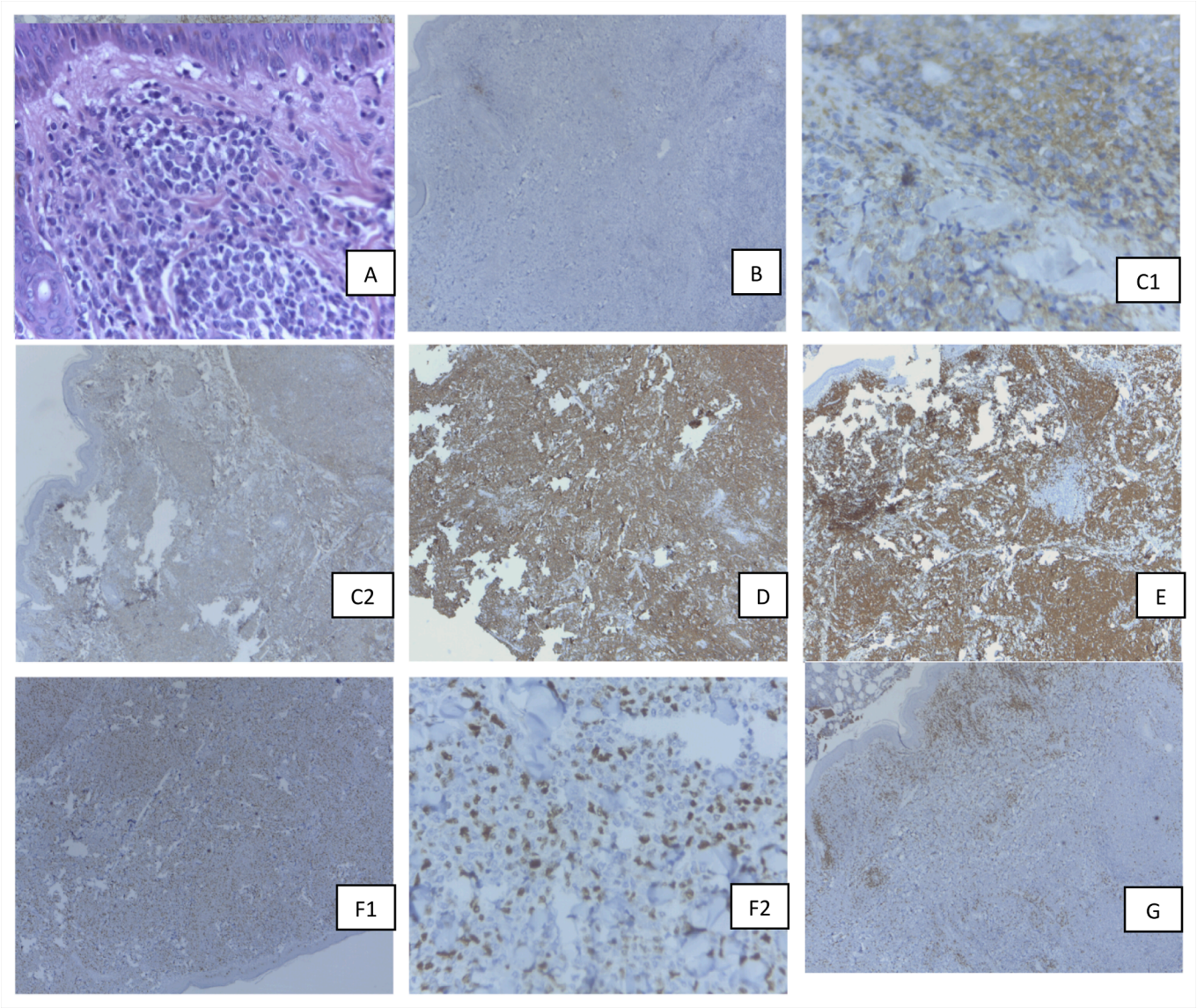

Fig. 2. (A) Biopsy with Hematoxylin-Eosin 40x tumor tissue sample neoplastic proliferation in the dermis, without infiltration of adnexa. Immunohistochemistry showed results of tumor cell phenotype (B) CD20 negative, (C1 and C2) CD4 positive, (D) CD56 positive, (E) TCL1 positive, (F1 and F2) Ki-67 at 60% and (G) CD 3 negative.

Significant lymphadenopathies in the right external iliac chain and right inguinal region were found on multi-slice spiral computed tomography scans. These typical secondary lesions were considered as inguinal metastasis.

The child had a prior biopsy in the highlands, but it was insufficient tissue and INEN's oncology pediatric team performed a new biopsy. Hematoxylin and eosin staining and immunohistochemical markers were studied. It showed CD4+ and CD56+; staining for more specific markers resulted in a local TdT+, CD45+, TCL1+ and CD34 -. In addition, the KI-67 score was 60% (Fig. 2).

Bone marrow compromise and leukemic expression can appear even without skin lesions in 60–90% of cases [3,4]. In this child, even after two years of evolution before the diagnosis, there was no bone marrow infiltration. Extramedullary manifestations include involvement of the liver, lymph nodes (40%−50%), sinuses, orbits and central nervous system, rarely splenomegaly (20%) and fulminant leukemia (5–25%) [3, 4], in this case only lymph node involvement was registered (right inguinal). It has also been documented that thrombocytopenia, anemia and, to a lesser extent, neutropenia can appear as hematologic disorders [4]. On the contrary, this patient's initial laboratory values were within normal parameters.

Treatment of BPDCN in pediatric patients is still controversial. Even if some intents have been made to create a treatment regimen [16], a gold standard is still far away. Most cases report good response with the same regimen used for ALL, recording remission rates of 93%, compared to 77% of the regimen for chronic myeloid leukemia and 80% of the treatment for lymphoma [3, 6, 16]. The most favorable results are usually seen in patients without skin involvement [4]. AL-like regimen includes prophylaxis of the nervous system with intrathecal chemotherapy, since it is considered one of the main causes of morbidity and mortality in patients with this disease [12]. Bone marrow transplantation is usually reserved for cases with one or multiple relapses; in elderly patients is also used as a consolidation therapy after chemotherapy, and it has shown to reduced disease relapses, especially allogenic hematopoietic stem cell transplant [8,11,15,17]. However, in pediatric patients it does not improve survival [3]. In this patient, institutional HR-ALL was given with good results, adding to the literature its efficacy in a different sociodemographic setting [18].

Various studies identify skin involvement as the initial manifestation (76% of adults and 79% of children) and also the most frequent [3].

These lesions are often asymptomatic and purplish or erythematous in appearance; however, they can also be pseudo-purple, plaque, nodular, equimotic, scaly or ulcerated [12]. The most compromised regions are usually the face, scapular region and to a lesser extent the trunk and extremities [4]. In this pediatric case of BPDCN, skin involvement was exclusively appendicular, it compromised soft tissue (solid tumor) and had a loco-regional presentation in the lower right limb (inner side of the right leg with a purplish tone). In adults, a disseminated form with or without skin involvement has been associated with a poorer overall and progression free survival rates [8].

4. Conclusion

To our knowledge, this is the first case report of BPDCN in a Hispanic child outside the US, which adds information about its course in this ethnic group. BPDCN is a diagnostic and therapeutic challenge in pediatrics, especially in the presence of nodular skin lesions from slow and progressive growth that does not seem to cause discomfort.

The decision of the oncology pediatric team was based on literature and similar unpublished cases from the institution. Emphasis should be placed on timely diagnostic through the use of immunohistochemical markers. The treatment of BPDCN with an institutional high-risk ALL regimen has reached very good results in this pediatric case, achieving a 37 month overall and progression-free survival to date.

5. Author contributions

All authors contributed and critically revised the manuscript. The authors would like to thank Melvi Guerrero Quiroga MC from the Pathology department of INEN for her assistance with Histopathology's images, as well as the breast and soft tissue department for the biopsy results.

6. Ethics statement

Informed consent was signed by the patient's proxy.

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CRediT authorship contribution statement

Katy Ordoñez Tanchiva: Conceptualization, Data curation. **Pamela Contreras Chavez:** Formal analysis, Investigation, Writing – review & editing. **Silvana Lucero Loli Guevara:** Project administration, Resources, Writing – original draft. **Carlos Rodrigo Quispe Vicuña:** Software, Supervision. **Neharika Bhardwaj:** Validation, Visualization. **Frederick Lansigan:** Writing – review & editing. **Erik Deconinck:** Writing – review & editing.

Declaration of Competing Interest

The authors declare no conflict of interest.

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