Bumps of Blood Cells: Blastic Plasmacytoid Dendritic Cell Neoplasm in an Elderly Filipino

Christian Bernard T. Cheng, M.D.*; Ellen M. Gatchalian, M.D.*; Flordeluna Z. Mesina, M.D.*; and Alejandro Arevalo, M.D.**

Abstract

Introduction: Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and aggressive hematologic malignancy derived from the precursors of plasmacytoid dendritic cells. This malignancy presents with various noticeable cutaneous lesions and usually occurs in elderly males. Cutaneous manifestations usually precede leukemic dissemination to the lymph nodes, bone marrow, and peripheral blood which is associated with poor prognosis.

Case presentation: We present a case of a 60-year-old Filipino male with a four-month history of multiple hyperpigmented, reddish brown, firm, fixed, non-tender cutaneous nodules on the extremities, trunk, chest, and face. Two large masses was also noted on the left arm and left upper back..Tissue biopsy of the cutaneous mass showed Immunohistochemical stain findings positive for LCA, CD68, CD4, CD56, and CD123 which are compatible with BPDCN. Patient was initially asymptomatic with relatively normal blood count and was treated supportively but serial blood count monitoring showed worsening with progression to acute myelogenous leukemia. Patient was then started on the 7+3 protocol of cytarabine and idarubicine which provided flattening of the cutaneous nodules and improvement of blood counts. However, due to complications of the disease and the treatment, the patient succumbed to severe pulmonary infection and sepsis.

Discussion: Due to the varied, non-specific cutaneous manifestations and the similarity in the morphology of the skin lesions with other cutaneous conditions along with the rarity of this disease, there is difficulty in establishing the diagnosis of BPDCN as well as standardizing its treatment. Immunohistochemical stains play an important role in confirming the diagnosis as well as ruling out other differential diagnoses to tailor appropriate treatment.

Conclusion: Blastic plasmacytoid dendritic cell neoplasm (BPDCN) generally has a poor prognosis owing to the rapidity of its spread to the bone marrow and peripheral blood. Early diagnosis is essential to initiate early therapy and prevent progression.

Keywords: blastic plasmacytoid dendritic cell neoplasm; cutaneous nodules; acute myelogenous leukemia; case report

Introduction

Cutaneous nodules are often secondary to an inflammatory or an infectious cause but on rare occasions are due to paraneoplastic manifestations of systemic malignancies including hematologic neoplasms. Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a very rare and aggressive hematologic malignancy that originates from the precursors of plasmacytoid dendritic cells.[1] BPDCN usually presents with cutaneous lesions that can be confused with other diseases. Owing to its rarity and various clinical manifestations, misdiagnosis is common and no standardized management is currently available. We report a case of a 60-year-old Filipino male with a four-month history of multiple hyperpigmented, purpuric, firm, fixed, non-tender cutaneous nodules on the extremities, trunk, chest, and face with note of two large masses on the left arm and left upper back which on work ups was compatible with a hematodermic neoplasm specifically BPDCN.

* *Department of Internal Medicine, Cardinal Santos Medical Center, San Juan City, Philippines*
** *Department of Pathology and Laboratory Medicine, Cardinal Santos Medical Center, San Juan City, Philippines*

Corresponding author: Christian Bernard T. Cheng, M.D., Cardinal Santos Medical Center, San Juan City, Philippines
Email: cbcheng15@yahoo.com

Case Presentation

A 60-year-old Filipino male consulted in our institution due to multiple hyperpigmented, purpuric, firm, fixed, non-tender cutaneous nodules on the extremities, trunk, chest, and face with note of two large masses on the left arm and left upper back. The said lesions were noted four months prior to consultation and initially presented as pruritic, hyperpigmented, erythematous patches on the left arm and forearm. The patient did not have fever episodes, cough and colds, body weakness and weight loss. The skin lesions

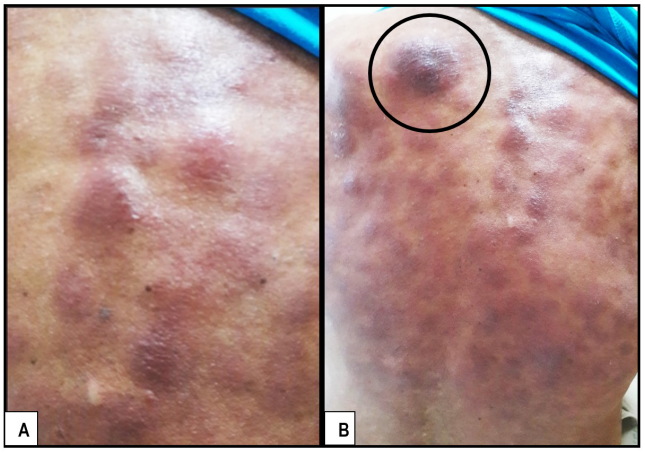

Figure 1. (A) Multiple hyperpigmented, purpuric, firm, fixed, nontender cutaneous nodules on the back (B) Hyperpigmented, firm, fixed nontender mass on the left upper back measuring 5 x 4cm

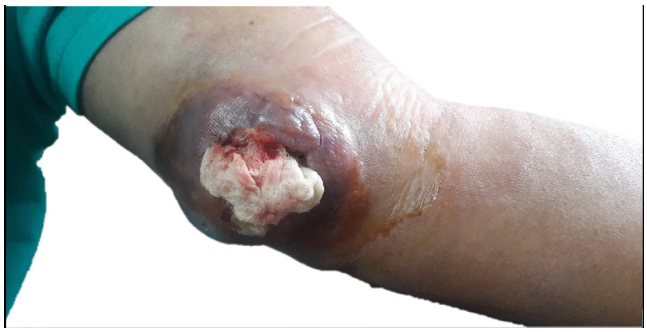

Figure 2. Mass on the medial surface of the distal third of the left arm measuring 6 x 4 x 3 cm. Patient underwent core needle biopsy and a gauze is seen in the middle.

were initially managed as a case of a viral exanthem and was treated supportively.

The erythematous patches gradually evolved into cutaneous nodules with some nodules coalescing into masses, the largest of which is located on the left arm and left upper back. Physical examination on consult showed hyperpigmented, firm, well-delineated, fixed, non-tender nodules on both upper extremities, trunk, chest, and face (Figure 1A). There were two masses measuring 5x4 cm on the left upper back (Figure 1B) and 6x4x3 cm on the left arm (Figure 2). Multiple cervical and axillary lymph nodes were palpated measuring approximately two to three centimeters. Lung and cardiac findings were unremarkable. Abdominal findings were normal except for a palpable splenic edge four to five centimeters below the left subcostal margin. Initial consideration at this time was a soft tissue malignancy with concomitant lymphoproliferative disease such as lymphoma because of the multiple palpable lymph nodes and palpable splenic edge.

The patient was admitted for evaluation. Initial complete blood count showed erythrocytosis with a hemoglobin of 197 g/dl, hematocrit of 58%, leukocytosis with WBC of 10.9 x 10^9/L (73% segmenters, 17% lymphocytes, 9% monocytes, and 1% eosinophils), platelet count was elevated at 627 x 10^9/L, serum

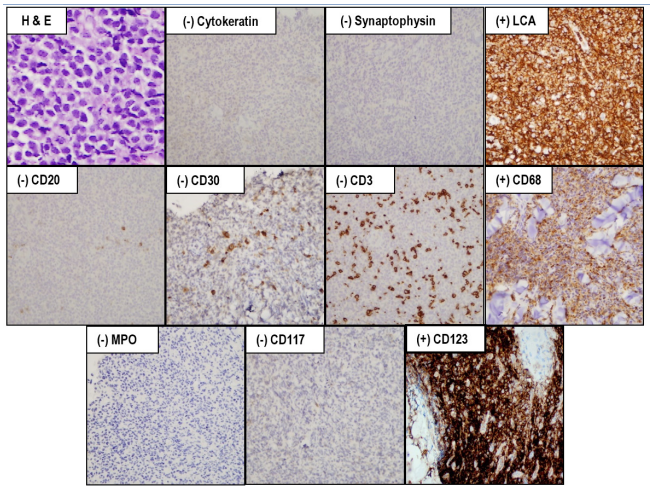

Figure 3. Immunohistochemical stains on the left arm mass: (A) Hematoxylin and Eosin showing dermal infiltrates of small round blue cells with prominent vesicular nucleoli and prominent mitotic activity, (B) negative Cytokeratin, (C) negative Synaptophysin, (D) positive LCA/CD45, (E) negative CD20, (F) negative CD30, (G) negative CD3, (H) positive CD68 with characteristic cytoplasmic dot-like pattern, (I) negative MPO, (J) negative CD117, and (H) positive CD123. CD4 and CD56 photomicrographs are not available at this time but both showed positive stains.

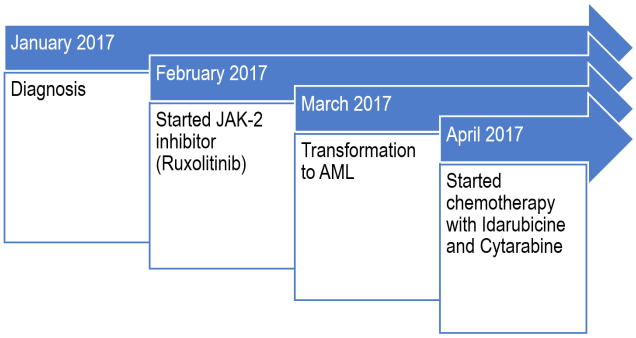

Figure 4. Timeline of diagnosis, intervention, and outcome

lactate dehydrogenase was twice elevated at 492units/L. Computed Tomography scan of the chest and abdomen showed non-specific, non-calcified subcentimeter nodule in the right upper lobe, bilateral axillary lymphadenopathies, normal sized liver, moderately enlarged spleen (splenic index of 999) and non-specific mildly enlarged lymph nodes in the porta hepatis, retroperitoneal para-aortic, and aorto caval space, mesenteric and bilateral inguinal regions.

A core needle biopsy of the arm mass was done with an initial result of small round cell tumor with neuroendocrine features and was sent for further immunohistochemical studies. Initial immunohistochemical stains showed positive for LCA and CD68 with negative stains for cytokeratin, synaptophysin, myeloperoxidase, CD3, CD20, CD117, and CD30 (Figure 3). This was signed out as 1) extramedullary myeloid tumor (myeloid sarcoma) vs. 2) cutaneous involvement by a monocytic leukemia. Bone marrow aspiration and biopsy done showed: markedly hypercellular bone marrow (More than 95%) with granulocytic and megakaryocytic hyperplasia, megakaryocytic pleomorphism

with atypia; Grade 2 reticulin fibrosis and focal collagen fibrosis indicative of a myeloproliferative neoplasm. Other tests done showed positive JAK-2 mutation assay and negative BCR-ABL mutation. The comprehensive leukemia panel showed no acute leukemic blast cell population. Patient was initially treated as a case of myeloproliferative neoplasm - polycythemia vera based on bone marrow aspiration findings and result of JAK-2 mutation assay and given supportive treatment with a JAK-2 inhibitor (ruxolitinib 10 mg/tab, one tablet twice a day) which resulted to flattening of the cutaneous nodules and improvement in the blood counts. Further immunohistochemical stains requested namely CD4, CD56, and CD123 all showed positive stains confirming a hematodermic neoplasm compatible with BPDCN (Figure 3).

The patient was apparently well until four weeks after, there was noted leukocytosis at 55.3 x 10^9/L with shift towards immature WBC and progressive increase in the blast counts. At this time the consideration was blastic transformation to acute myelogenous leukemia (AML). A repeat comprehensive leukemia panel showed acute leukemia of ambiguous lineage consistent with a blast population showing myelo-monocytic and NK-cell differentiation wherein the main considerations are: BPDCN vs AML. The patient was immediately started on continuous induction chemotherapy using the 7+3 regimen of cytarabine and idarubicine for four weeks with supportive transfusions (Figure 4). Initial courses of the chemotherapy were tolerated but the patient eventually developed febrile neutropenia and succumb to severe pulmonary infection and sepsis.

Discussion

This case exemplified the dynamic nature of hematologic malignancies. The lesions started as nonspecific diffuse cutaneous nodules and soft tissue masses progressing into full-blown AML. At the onset, we have encountered a diagnostic dilemma as there are several differential diagnoses for small round cell tumors. Looking at the morphology of the abnormal infiltrating cell in the dermal layer, the following were considered 1) undifferentiated carcinoma; 2) carcinoma with neuroendocrine features; and 3) non-hodgkin's lymphoma (NHL). With the immunohistochemical stain findings of negative cytokeratin and synaptophysin, the first two were ruled out. Leukocyte common antigen was positive which led us to consider lymphoproliferative diseases. IHC were done for further classification which resulted to (-) CD20, (-) CD3, and (-) CD30. These findings are suggestive of a possible non-lymphoid hematologic tumor. Additional IHC were requested particularly CD68, myeloperoxidase (MPO) and CD117 to rule out 1) myeloid sarcoma (MS), 2) BPDCN, and 3) histiocytic sarcoma. Results showed (+) CD68, (-) MPO, and (-) CD117 which are compatible with either MS of monocytic lineage or BPDCN. Clinically and histologically these two hematopoietic malignancies with tropism to the skin are difficult to distinguish. Both are relatively rare neoplasms with well-characterized cell of origin.[2] MS, also referred to as granulocytic sarcoma or extramedullary myeloid tumor, occurs at any site of the body, although the most common sites are the lymph nodes, skin and soft tissues, testes, bone, peritoneum, and the gastrointestinal tract.[2,3] MS may initially manifest as skin lesions and can be associated with concurrent or antecedent acute leukemia in the bone marrow. MS can present as an erythematous rash, urticaria, purpura, or maculopapular eruptions making the lesions difficult to differentiate from BPDCN and other diseases thus the need for a histopathologic and Immunohistochemical studies.[1]

Blastic plasmacytoid dendritic cell neoplasm (BPDCN), previously known as blastic NK lymphoma, agranular $CD4^+$ NK cell leukemia, and agranular $CD4^+/CD56^+$ hematodermic neoplasm is a hematologic neoplasm derived from the precursors of plasmacytoid dendritic cells. It is a rare and highly aggressive lymphoma/leukemia mostly presenting with cutaneous manifestation mostly found among elderly males aged 60-70 years old. The neoplasm is rare, accounting for less than 0.8% of all cutaneous lymphomas and less than one percent of all acute leukemias.[4] Cutaneous manifestations are prominent and usually precede leukemic dissemination to the lymph nodes, bone marrow, and peripheral blood.[1] Cutaneous manifestations are variable and include erythema, papules, patches, plaques, or tumor nodules with erythematous to bruise-like discoloration. Majority of the patients would present initially with isolated skin lesions followed by dissemination but there were also reports of association with another myeloid neoplasm that might precede, occur with, or follow BPDCN.[1,3] The very strong skin tropism of BPDCN is likely related to the skin-homing properties of cutaneous lymphocyte-associated antigen (CLA/CD162).[3] Cutaneous manifestations are usually characterized by a diffuse and dense monomorphous infiltration in the skin of medium-sized cells with a blastic morphology. The blastic tumor cells display nuclei with fine-dispersed chromatin and a sparse cytoplasm.[5] The clinical presentation varies from one or two skin nodules or tumors to disseminated cutaneous spread. They can be in the form of 1) brown or purple nodular lesions (73%); 2) "bruise-like" brown to violaceous infiltrated patches (12%); or 3) disseminated and mixed lesions (14%).[6]

Histologically, both MS and BPDCN exhibit medium to large atypical, blast-appearing cells with high nuclear-to-cytoplasmic ratio, irregular nuclear membranes, fine chromatin, prominent nucleoli, agranular, and increased mitotic activity. The cells are arranged in aggregates and diffuse sheets and the epidermis is spared.[2-5] Myeloperoxidase staining is positive in 66-96% of MS, other markers of MS

include CD43, CD68, lysozyme, CD117, CD11c, CD13, and CD33.[1] According to Sangle et al.,[3] positive staining for CD4, CD56, CD123, TCL1, and MxA showed a significant positive correlation with BPDCN. Positive staining for myeloperoxidase and lysozyme or negative staining for CD4, CD56, CD123, MxA, or TCL1 was associated with MS. CD68 and lysozyme is the most consistently expressed and sensitive immunohistochemical stains in MS. Myeloperoxidase is considered to be a specific marker but is positive in only 58% of cases.[3] BPDCN are always MPO negative. CD68 immunostaining shows a distinct pattern of cytoplasmic dot-like pattern in BPDCN.[7] According to an article by Dr Pemmaraju, the classic IHC panel of BPDCN are (+) CD4, (+) CD56, and (+) CD123 with (+) TCL-1.[8] As applied to our patient, with the IHC results showing negative stains for myeloperoxidase and positive stains for CD4, CD56, and CD123, the lesions point more to BPDCN.

Optimal treatment of BPDCN is unknown as there are few data available to guide treatment. Treatment is non-standardized and currently there is no consensus owing to its rarity. Patients usually are treated with regimens similar to AML, acute lymphoblastic leukemia (ALL), or aggressive NHL depending on the clinician's choice.[8] One multicenter study showed higher complete remission and overall survival rate upon using ALL/lymphoma regimen than with an AML-type regimen (median survival of 12.3 months versus 7.1 months).[5] Similarly, several reports demonstrate that lymphoid-like chemotherapy is currently the best treatment option for BPDCN, achieving high response rates.[9] Allogeneic hematopoietic cell transplantation (HCT) as a form of therapy to induce complete remission in adult patients with BPDCN has been long considered. The median overall survival for patients treated with conventional therapy is usually 12-14 months, while patients receiving allogeneic HCT have a median survival of almost 23 months and a three-year cumulative overall survival of 40-50 percent.[10]

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) has a poor diagnosis as it rapidly extends to the bone marrow and peripheral blood and rapidly progress to a leukemic phase. Based on Gurbuxani et al,[10] the following were considered factors predictive of a good outcome: a younger age (<40yo); ALL-like induction therapy; and presence of immature cells.[9]

Conclusion

In this paper, we have presented a rare cause of diffuse cutaneous nodules that preceded the development of AML. In the evaluation of hematologic malignancies presenting as diffuse cutaneous nodules, immunohistochemical stains play an important role in differentiating further the origin of the hematologic cells. BPDCN generally has a poor prognosis because of its aggressiveness in spreading to the bone marrow and peripheral blood progressing into the leukemic phase. Appropriate and timely tests are needed to confirm the diagnosis, initiate early therapy and prevent progression of the disease.

Informed consent: The patient and his wife verbally gave consent to publish this case report while ongoing chemotherapy treatment.

Disclosure: None to declare

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Appendix

Table I. Some case reports along with the noted cutaneous manifestations, immunohistochemical stains, management, and prognosis

Author/Year	Patient	Manifestation/s:	Management	Status
Pennisi M, Cesana C, Cittone M, Bandiera L, Scarpati B, Mancini V, Soriani S, Veronese S, Truini M, Rossini S, Cairoli R. (2017).[8]	37/M	Skin lesions, hearing loss, nose bleeding, visual impairment, and headache. Conjunctival bleeding, brown nodular bruise-like lesions on the scalp, neck, and back, and bilateral cervical and submandibular lymph nodes enlargement. No hepatosplenomegaly. Hypertrophic obstruction of the rhinopharyngeal tract Positive for CD4, CD10, CD56, CD99, CD123, CD303, TdT, BCL2 Negative for CD3, CD5, CD8, CD20, CD30, CD34, CD79a, CD117, CD138, MPO, TIA1, PAX5, CyclinD	Hyper CVAD (Cyclophosphamide, vincristine, Adriamycin) and dexamethasone and intrathecal prophylaxis (methotrexate, cytarabine, and methylprednisolone) x 3 courses with allogeneic hematopoietic stem cell transplantation (HSCT)	Alive
CY Lin, MY Wu, TT Kuo, and PH Lu. (2017).[1]	86/M	Nodular plaques on scalp Erythematous and violaceous nodular plaques on the parietal and temporal scalp Positive for CD4, CD33, CD56, CD68 (KP1), CD123, and TCL-1 Negative for CD3, CD20, CD10, Bcl-6, CD30, ALK, myeloperoxidase, lysozyme, and granzyme B	Palliative oral prednisolone (30 mg/d)	Died
Jabbour R, Doumit J, Maddah J, and Nasr F. (2014)[2]	67/M	Fatigue, weight loss, and cough with hepatosplenomegaly, multiple palpable bilateral axillary and inguinal lymph nodes Positive for CD5, CD10, CD3, CD7, CD123 and TCL-1 Negative for CD34, TdT, CD20, CD38, CD57, PAX-5	Cyclophosphamide, Hydroxydaunorubicin, Vincristine, and Prednisone (CHOP) x 4 cycles	Alive
Roodbergen S, Hofland J, Lam K, Dikrama P, Broyl A and Monkhorst K. (2013)[3]	58/F	Violaceous nodule over the right scapula Positive for CD2, CD3, CD43, CD4, tdt, CD56, CD68, and CD123 Weakly positive for CD33 and CD38	Daunorubicin and Cytarabine followed by allogeneic haematopoietic stem cell Transplantation and Intrathecal Methotrexate and Dexamethasone	Alive
Angelot-Delettre F and Garnache-Ottou F (2012)[4]	81/M	Multiple brown-red plaques on the face, abdomen, and back and asthenia Positive for CD4, CD56, CD303, CD304, CD123 and TCL1 Negative for CD34 or TdT	Course of chemotherapy	Died
Lencastre A et al. (2012)[5]	76/M	Multiple violaceous plaques and nodules on the face and scalp Positive for CD4, CD43, CD45, CD56, CD123 and HLA-DR Negative for CD3, CD5, CD8, CD20, CD30, CD34, CD38, CD117, TDT, myeloperoxidase, light IgG chains and PAX5	CHOP (cyclophosphamide, adriamycin, vincristine, and prednisolone) x 6 cycles	Died
Munoz J, Rana J, Inamdar K, Nathanson D, Janakiraman N. (2012)[6]	66/F	Left forearm soft tissue swelling Positive for CD4 and CD56	Induction therapy with Cytarabine and Idarubicin Reinduction chemotherapy with Mitoxantrone, Etoposide, and Cytarabine	Died
Shieh MP, Reisian N, Walavalkar V, Slater L, and Lambrecht N. (2012)[7]	65/M	Violaceous cutaneous lesions, generalized lymphadenopathy, and pancytopenia Positive for CD4, CD56, and CD123	Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) x 8 cycles Bortezomib, Dexamethasone, and Thalidomide	Died
Chen JP, Zhou JY, Qin DB, Xu SN, and Yan XC. (2010)[8]	20/M	Nodules on the right thigh, trunk, and limbs Positive CD4, CD34, CD43, CD56, CD99 Negative CD3, CD20, CD57, TdT, MPO	Etoposide, Cyclophosphamide, Vincristine, Prednisone, and Methotrexate Mitoxantrone, Cyclophosphamide, Vincristine, and Dexamethasone	Died

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