JPDS Journal of the Philippine Dermatological Society

CASE REPORT

Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma in a 76-year-old Filipino Male: a case report

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ABSTRACT

INTRODUCTION Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (PCAECTCL) is a rare subtype of cutaneous T-cell lymphoma characterized by widely distributed ulcerated lesions, epidermotropic infiltrates of CD8+ cytotoxic T cells, aggressive course, high tendency to spread to extranodal sites, poor response to conventional therapies and unfavorable prognosis.

CASE REPORT We report a 76-year-old Filipino male presenting with eight-month history of erythematous scaly patches evolving into widespread ulcerated nodules, unresponsive to topical and systemic steroids. Histopathology revealed prominent epidermotropism and lichenoid infiltrate of atypical lymphocytes. Immunohistochemistry showed positivity for CD3, CD8, Ki67 (5-15%), CD7, CD2; indeterminate for TIA-1, with high background staining; and was negative for CD20, CD30, CD4, CD5, CD56, granzyme-B, TdT, Epstein-Barr encoding region in situ hybridization (EBER-ISH), consistent with PCAECTCL. No overt metastasis was detected. The patient underwent interferon alfa 2B therapy followed by three full cycles of CHOP chemotherapy. Improvement was seen as thinning of plaques and nodules and re-epithelialization of ulcers however, severe anemia and leukopenia ensued with therapy. He then succumbed to septic shock secondary to pneumonia during the height of the COVID-19 pandemic.

CONCLUSION This case emphasizes that despite accurate diagnosis, polychemotherapy, and favorable response to therapy, complications may still arise contributing to the poor prognosis and low five-year survival rate of this condition.

KEYWORDS T-cell lymphoma, CD8 positive, neoplasms

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Conflict of interest
None

Source of funding
None

Cite as
Canlas-Estrella KM, Arcaira JA, Legarda-Montinola F, Dumagay TE. Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma in a 76-year-old Filipino Male: a case report. J Phil Dermatol Soc. 2022;31(1):37-41.

INTRODUCTION

Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (PCAECTCL) is a particularly rare type of lymphoma known by its belligerence and poor prognostic outcome.[1] The paucity of cases has led to roadblocks in arriving to its diagnosis. Lack of established criteria render this condition to be in a provisional non-specified category of the World Health Organization European Organization for Research and Treatment of Cancer (WHO-EORTC).[2]

PCAECTCL is more commonly seen among elderly males presenting as generalized papules, plaques, and nodules that often erode and ulcerate. Histopathology typically shows prominent and nodular to diffuse infiltrates of atypical lymphocytes. Immunohistochemical (IHC) profile demonstrates CD3, CD8, CD7, CD45RA, β-F1, and TIA-1.[3] It remains to be a therapeutic challenge as most cases achieve a partial response.

In this case report, we present PCAECTCL occurring in an elderly Filipino male with positive response to chemotherapy, but unfortunately succumbed to pneumonia at the height of the COVID-19 pandemic.

CASE REPORT

A 76-year-old Filipino male presented with an eight-month history of generalized, pruritic erythematous patches and scaling. He had a background of colon cancer stage I, status post hemicolectomy and re-anastomosis, and familial history of breast cancer on the maternal side. No chemotherapy or radiation was administered post-surgery. He sought consult with a dermatologist who initially managed him as a case of exfoliative dermatitis but was unresponsive to oral and topical steroids. After three (3) months, patches evolved into plaques and nodules, some with ulcerations (Figure 1). Likewise, he developed intermittent fever episodes, loss of appetite, and generalized body weakness. No palpa-

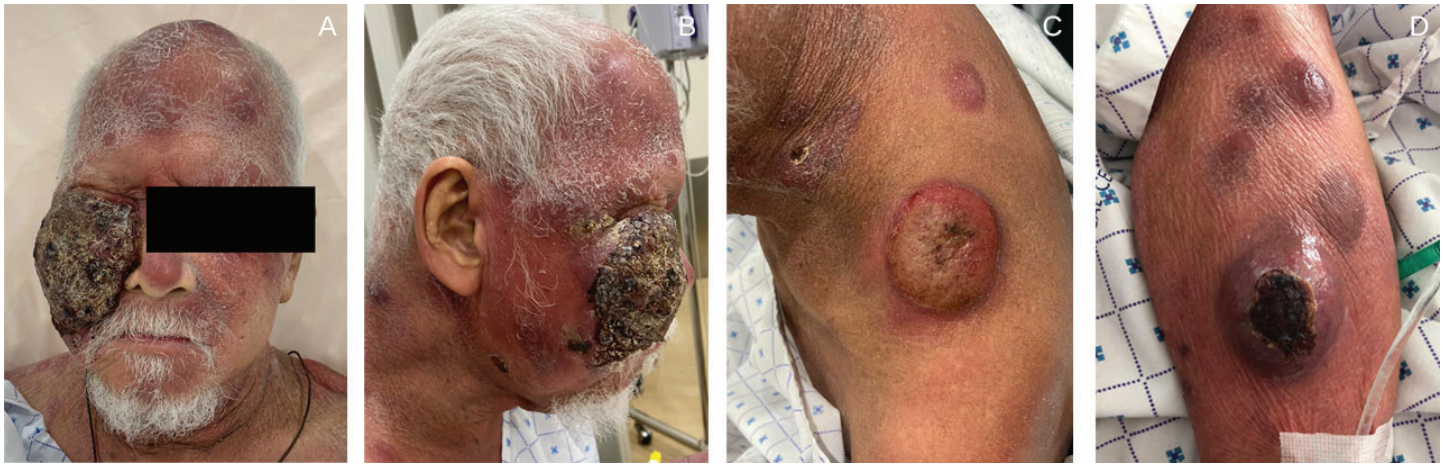

Figure 1. **A-B.** Physical examination revealed multiple darkly erythematous to violaceous nodules topped with hemorrhagic crusted erosions on the face, **C.** trunk and **D.** extremities. **B.** With the largest nodule measuring about 12x10cm on the right cheek. Multiple erythematous to violaceous patches and scaly plaques on the face, trunk, and extremities were also noted.

ble lymph nodes were detected at this time. A single skin punch biopsy was done on a nodule on the back which revealed focal epidermotropism and a heavy lichenoid infiltrate encompassing the entire dermoepidermal junction and papillary dermis, composed of medium to large atypical lymphocytes showing pleiomorphism, hyperchromatic nuclei, prominent nucleoli, and several nucleoli. These atypical infiltrates were also present in the reticular dermis, surrounding blood vessels and adnexal structures. No necrosis nor destruction of vessels or follicles was seen. The attending dermatopathologist initially signed out the case as a lymphoproliferative disorder warranting a more in-depth work-up.

Further IHC staining showed the following profile: positive for CD3, CD8, Ki67 (5-15%), CD7, and CD2; indeterminate for TIA-1, with high background staining; negative for CD20, CD30, CD4, CD5, CD56, granzyme-B, TdT, and EBER-ISH (Epstein Barr encoding region- in situ hybridization). With these, a diagnosis of primary cutaneous aggressive epidermotropic CD8+ positive T-cell lymphoma was made. An attempt for staging was done using computed tomography scans of the head, chest, and abdomen which revealed non-calcified pleural and subpleural nodules in both upper lobes and prominent axillary lymph nodes. Elevated lactate dehydrogenase levels were noted. No suspicious lesions were visualized in the brain or visceral organs. Due to financial constraints, the patient was not able to pursue further laboratory work-up such as peripheral blood smear to detect presence of atypical lymphocytes in the bloodstream, positron emission tomography (PET) scan to evaluate for possible extranodal metastasis, or lymph node biopsy to check for nodal involvement.

The patient was placed on narrowband UVB phototherapy two (2) to three (3) times a week and managed alongside an oncologist. Whilst he was still undecided for chemotherapy, he

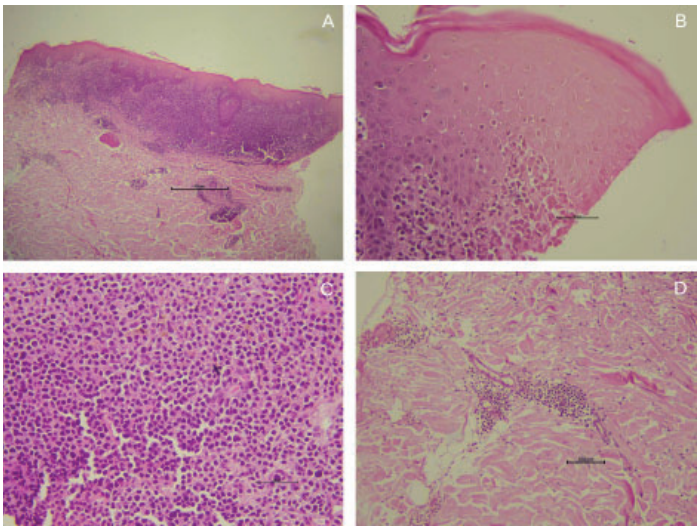

Figure 2. Histopathology findings revealed an epidermis showing orthokeratosis, acanthosis, with some focal epidermotropic lymphocytes (**A.** H&E 40X, **B.** H&E 400X). The entire dermoepidermal junction and papillary dermis showed a heavy lichenoid infiltrate of atypical lymphocytes (**C.** H&E 400X) admixed with melanophages. Patchy lymphocytic infiltrates were present in the reticular dermis surrounding blood vessels, eccrine ducts (**D.** H&E 400X) and glands.

was started on interferon alfa-2B subcutaneous injections three (3) times a week for six (6) doses and was subsequently lost to follow-up. Minimal improvement was noted. When he returned for consult, he was then started on CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy regimen with supportive pegylated-GCSF, with the intention of reassessing for hematopoietic stem cell transplant or novel agents after four (4) cycles. He only tolerated three complete cycles of polychemotherapy even though supportive therapy with filgras-

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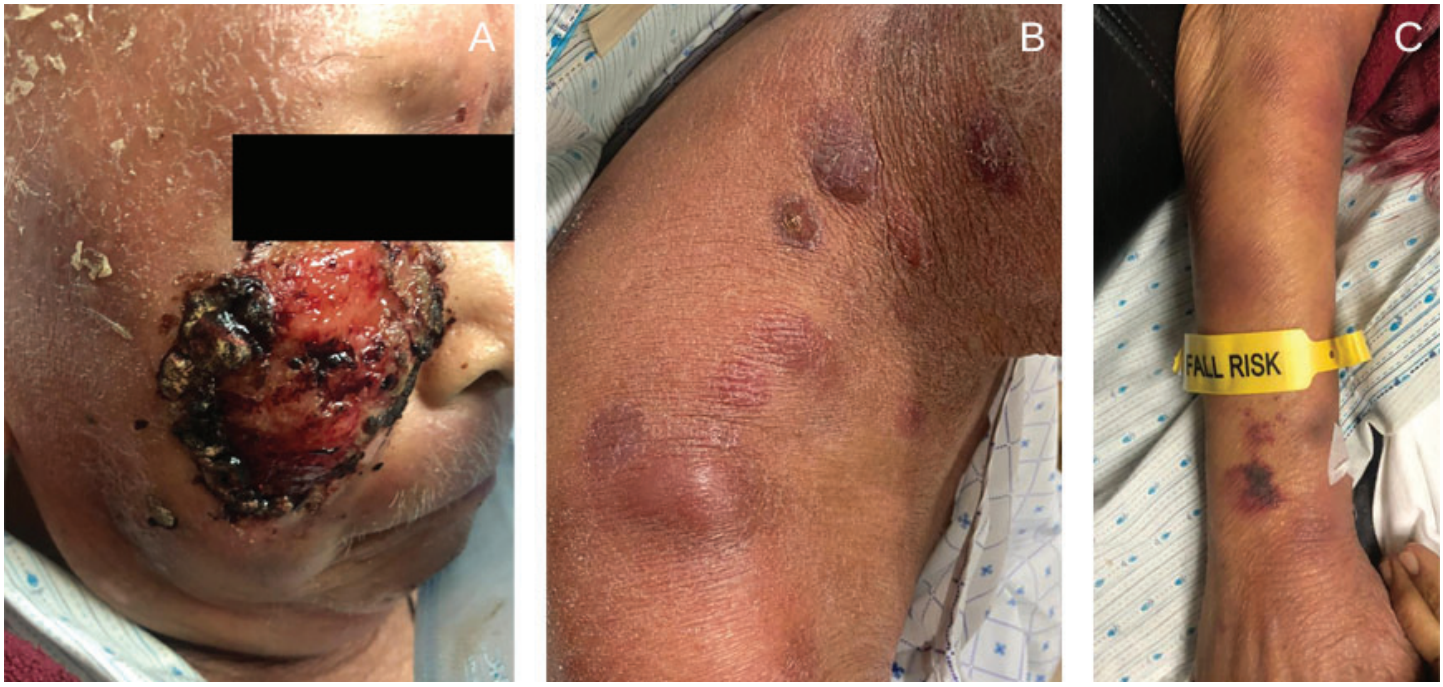

Figure 3. A. During his third chemotherapy session, significant improvement in skin lesions were noted, most remarkably on that of his right cheek that markedly decreased in thickness. **B-C.**Other skin lesions on the trunk and extremities have become darkly erythematous and ulcers have begun to re-epithelialize.

tim was given. During his 4th cycle, only vincristine was administered because of severe anemia and leukopenia. Improvement of skin lesions was noted described as decrease in size, flattening of nodules and plaques, and beginning re-epithelialization of erosions and ulcers (Figure 3).

Unfortunately, despite promising response to therapy, the patient's immunocompromised state predisposed him to secondary infections and developed pneumonia. However, as this occurred during the height of the pandemic, he was initially managed as a case of COVID-19 suspect and eventually succumbed to septic shock secondary to pneumonia in immunocompromised host. His COVID-19 RT-PCR result came back negative, albeit post-mortem.

DISCUSSION

Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (PCAECTCL) comprises less than 1% of all cases of CTCL.[2] Most are elderly males, manifesting clinically with progressive, widespread ulcerated or crusted papules, patches, plaques, nodules, and tumors. Evolution of lesions do not typically follow that of mycosis fungoides (patch, plaque, then tumor stages). Oral involvement is a poor prognostic factor but for our patient, he had no mucosal lesions. This condition is classified as a provisional non-distinct entity by WHO-EORTC due to the rarity and variability in clinical presentation.[3]

Diagnosis is established through histopathology , where consistent findings are epidermotropism and nodular to diffuse dermal infiltrates of pleiomorphic atypical lymphocytes, as was seen in our patient's specimen. Immunohistochemistry shows a CD8+/CD4- profile, with positivity for CD3, CD45RA, BF1, TIA-1, but negative for CD30 and CD45RO.[4] Although critical to establish positivity to CD8 with negative CD4 profile, it is important to note that CD8 positivity alone does not always have prognostic value. Some indolent types of CTCL may be CD8+, like CD8+ pagetoid reticulosis (Ketron-Goodman disease), CD8+ mycosis fungoides, and anaplastic large cell lymphoma. The impact of CD8+ on prognosis can be traced to activation of the TH1 pathway involving type I interferons. This has been elucidated in biopsy specimens of viral infections like herpes simplex, where TH1 response results in increased proliferation and recruitment of cytotoxic skin-homing lymphocytes.[5] In PCAECTCL, this is the postulated mechanism to which its aggressive nature comes from. Our patient noted rapid progression over the course of three months, from erythematous patches evolving into eroded nodules and tumors, and likewise exhibited the CD8+/CD4- profile. An increased Ki67 proliferation index (at least 20%) is also seen.[2] This index correlates with cells in active mitosis, thus denoting tumor progression. It is used as a marker of prognosis of several human cancers, including melanomas and lymphomas.[6]

Epidermotrophic T-cell lymphomas encompass a group of

rare atypical lymphoid disorders. The closest differential for our case would be a CD8+ phenotype of generalized pagetoid reticulosis (Ketron-Goodman disease), but this usually starts as a solitary patch or plaque on the distal extremities as opposed to our patient who had a generalized presentation. Despite similar histopathology, clinical history as well as testing for CD45RA, CD45RO, and T-cell receptor stains can help further delineate this condition but were unfortunately not available. Primary cutaneous anaplastic T-cell lymphomas may also share similar histology but are strongly CD30-positive, to which our patient was not, hence that was ruled out. Extranodal NK/T-cell lymphoma is commonly seen on the nose, which is spared in our patient, and is strongly positive to CD2, CD56, and negative for CD3. Our patient was positive for CD2, but was negative for CD56 and conversely positive for CD3, ruling this condition out. Furthermore, this condition is strongly positive for EBV in situ hybridization, which was found to be negative in our patient. Cutaneous γ/δ (gamma delta)-T cell lymphoma is an aggressive disorder presenting with plaques and tumors on the trunk and upper extremities. It may appear histologically similar to primary cutaneous aggressive CD8+ T-cell lymphoma but IHC stains for this condition would be positive for CD3, CD2, and CD56, and negative for CD4 and CD8. Our patient was positive for CD3, CD2, CD8, and negative for CD56 and CD4, hence that was ruled out. Ideally, GM3 and TCR-β-F1 immunostains would be positive for this condition but was not available for our patient.[7]

Accurate histopathologic correlation is needed to determine clinical course and response to therapy. To date, there is no single criterion that is pathognomonic alone for PCAECTCL.[3] Submission of multiple simultaneous biopsies from individual patients can enhance diagnostic accuracy.[8] Since our patient initially presented in an erythrodermic state, a biopsy may have not yet revealed clues towards the diagnosis of lymphoma. Interpretation of biopsy specimens from erythrodermic patients poses a challenge for pathologists because the microscopic manifestations of the underlying condition are subtle. Patients in erythroderma may have lesions in varying degrees of evolution, timing of doing the biopsy as well as careful selection of biopsy site and representative lesion are paramount in getting the highest yield in histopathology.

PCAECTCL has an increased tendency for systemic spread to extracutaneous sites such as the central nervous system, lungs, and testes. Lymph nodes are usually spared in contrast to classic mycosis fungoides.[3] Cases presenting with disseminated ulcerated plaques and nodules at the onset and rapid progression over time has been associated with metastatic spread. Our patient presented with an already widespread involvement at the time of consult, and on computed tomography showed subpleural nodules and prominent axillary nodes which may allude to beginning metastatic spread. Furthermore, it was suggested that patients with CD56 positivity is linked to increased tendency for metastatic spread.[9] Other indicators for higher incidence of systemic spread identified were angiocentricity and angioinvasion, expression of CD15, and CD7/CD21 phenotypes.[1] Our patient's specimen exhibited angiocentricity, which could have likely contributed to the propensity of spread to the pleura and lymph nodes.

All new patients diagnosed with cutaneous T-cell lymphoma should be overseen by a multi-disciplinary team of a dermatologist, oncologist, and pathologist to establish the diagnosis, staging, and management plan, as done with our patient. Examination should include documentation of skin lesions, careful palpation of lymph nodes and abdomen to check for visceral masses or hepatosplenomegaly. Laboratory work-up should include a complete blood count, CD4/CD8 ratio, check for Sezary cells, liver function tests, lactate dehydrogenase, serum urea, electrolytes, computed tomography of chest, abdomen, and pelvis for staging, lymph node biopsy (if with clinically palpable lymph nodes), and bone marrow aspiration.[10] Repeat examinations may be done if disease progression is suspected. The patient is at least T3 since he presented with tumors already, although no clinically apparent lymph nodes were palpated on physical examination, prominent axillary nodes were seen on computed tomography. Due to financial constraints, patient was not able to pursue further laboratory work-up such as peripheral blood smear to detect presence of atypical lymphocytes in the bloodstream, positron emission tomography (PET) scan to evaluate for possible extranodal metastasis, or lymph node biopsy to check for spread. Multiple skin biopsies can increase chances of clinching the diagnosis, as well as an ellipse or incisional biopsy, to allow more tissue for examination and immunohistochemistry.

Although the reported cases of PCAECTCL are few, the overall prognosis is quite poor, where only 7 of 45 were alive on their latest follow-up.[1] An average 5-year survival rate of 18% was noted by European cutaneous lymphoma groups.[2] Poorer outcomes were attributed to rapid metastasis, lower response rate to chemotherapy, and higher tendency to relapse.

Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (PCAECTCL) is a persistent therapeutic challenge due to scarcity of reported cases and lack of large randomized trials. These are indispensable in evaluating various treatment regimens, specifically their long-term efficacy. Conventional therapies for classical CD4+ CTCL are usually ineffective for PCAECTCL (such as topical steroids, UVB, PUVA, local radiotherapy, and interferon alfa) as these most often target the TH2 phenotype. With the paucity of guidelines, the most commonly used treatment options are adapted from lymphoma protocols, involving polychemotherapy with six (6) to eight (8) courses of CHOP or hyper-CVAD (hyper-cyclophosphamide, vincristine, doxorubicin, and dexamethasone), however, results are unsatisfactory and are associated with rapid recurrence.[8] The CHOP

regimen was noted to produce clinical remission in 38% of patients with a median response duration of 5 to 41 months.[11] Our patient was only able to tolerate three (3) complete cycles of CHOP, with the fourth being solely vincristine due to severe immunosuppression. Although there was improvement noted as decrease in redness and thickness of the lesions, he developed secondary bacterial pneumonia which led to his demise. A favorable response was noted by Gormley (2010) in their patient who received hyper-CVAD, who just after two (2) cycles achieved a dramatic response. After the sixth cycle, the patient was clear of lesions.[12] However, definite conclusions need further evaluation of efficacy, specifically for long-term remission and 5-year cure rates.[13] Novel therapies are promising and deliver variable results. A report by Cyrenne (2017) showed long-term remission in a refractory case after receiving brentuximab vedotin. This agent is a monoclonal antibody against CD30 antigen and is being explored for cases that fail to respond to conventional therapy. Response rates vary from 41-56% depending on the CD30 positivity.[14]

Autologous stem cell transplantation is another promising treatment option explored for PCAECTCL. In a series of patients who received stem cell transplantation following polychemotherapy, the overall survival rate among patients who received any type of transplantation (bone marrow or peripheral blood origins) was 55.6% at a median follow-up of 24 months.[15] Our patient was planned to undergo allogenic stem cell transplant depending on response to his course of polychemotherapy, however, he did not survive long enough for reassessment.

CONCLUSION

Primary cutaneous aggressive epidermotropic cutaneous T-cell lymphoma (PCAECTCL) remains to be a diagnostic and therapeutic challenge. Early detection and accurate diagnosis are key players to attain the best possible outcome for an already poorly responsive disease. This case proves that despite accurate diagnosis and favorable response to chemotherapy , there is still a fine line being trudged by both the patient and medical team in providing the appropriate treatment amidst possible complications. Overall, there are more questions still left unanswered with this debilitating, aggressive, and poorly responsive disease.

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