Int J Hematol (2009) 90:226–229
DOI 10.1007/s12185-009-0365-7

CASE REPORT

Differential diagnosis and treatment of primary, cutaneous, anaplastic large cell lymphoma: not always an easy task

Michael D. Diamantidis · Athanasios Papadopoulos · Georgia Kaiafa · George Ntaios · Georgia Karayannopoulou · Ioannis Kostopoulos · Fotios Girtovitis · Zoi Saouli · Zisis Kontoninas · Ioannis D. Raptis · Christos Savopoulos · Apostolos Hatzitolios

Received: 15 November 2008 / Revised: 27 May 2009 / Accepted: 1 June 2009 / Published online: 23 June 2009

Abstract Primary cutaneous anaplastic large cell lymphoma (PC-ALCL) is a rare and distinct neoplasm appearing de novo on the skin. We present a case of a 75-year-old man diagnosed with PC-ALCL in his left femoral region. We describe the morphology of lesions along with the differential diagnosis, treatment, clinical course and prognosis. We further discuss parameters concerning treatment that should be considered when a PC-ALCL is diagnosed. Our case report demonstrates the complexity in classification, staging, differential diagnosis and therapy selection of PC-ALCLs. It is crucial to emphasize the importance of clinical criteria in diagnosing a PC-ALCL in combination with immunohistochemistry.

Keywords Primary, cutaneous, anaplastic large cell lymphoma (PC-ALCL) · T-non-Hodgkin lymphoma (T-NHL) · $CD30^+$ lymphoproliferative disorder · Immunohistochemistry · CHOP regimen

The authors Michael D. Diamantidis and Athanasios Papadopoulos contributed equally to the manuscript.

M. D. Diamantidis (✉) · A. Papadopoulos · G. Kaiafa · G. Ntaios · F. Girtovitis · Z. Saouli · Z. Kontoninas · I. D. Raptis · C. Savopoulos · A. Hatzitolios
Department of Hematology,
First Propedeutic Department of Internal Medicine,
Aristotle University of Thessaloniki,
AHEPA Hospital, 1 S. Kiriakidi St,
546 36 Thessaloniki, Greece
e-mail: diamantidis79@yahoo.gr

G. Karayannopoulou · I. Kostopoulos
Department of Pathology, Aristotle University of Thessaloniki,
Thessaloniki, Greece

1 Introduction

Primary, cutaneous, anaplastic large cell lymphoma (PC-ALCL) is a rare T-cell lymphoma presenting on the skin and characterized by good prognosis and treatment response. It belongs to $CD30^+$ lymphoproliferative disorders, which cover a wide clinical and morphological spectrum of diseases including lymphomatoid papulosis (LyP) at one end and anaplastic large cell lymphoma (ALCL), either PC-ALCL or systemic ALCL, at the other end [1]. The incidence of PC-ALCL among other types of peripheral T-cell non-Hodgkin lymphomas (PTCLs) is 1.7% [1]. Therefore, PC-ALCLs are uncommon. Patients with PC-ALCL usually present with an asymptomatic, solitary skin tumor or nodule that may be ulcerated.

2 Case report

A 75-year-old man presented with a 2-month-history of two asymptomatic, cutaneous, reddish, enlarging tumors measuring 4 × 2 and 3 × 2.5 cm respectively, located on the left femoral region and a 2 × 1.5 cm nodule across them. The 2 larger tumors were adjacent to each other, forming an irregularly shaped mass of 7 × 2.5 cm with elevated borders (Fig. 1a). Ulcers or necrotic lesions were absent. Surgical removal of lesions had been attempted at his local health care unit, before his referral to our center. The surgical removal of the mass must have been incomplete, because 3 weeks after the operation, the tumors relapsed. CMV, EBV, HIV, HBV and HCV tests were negative. Skin biopsy revealed primary cutaneous anaplastic non-Hodgkin large cell lymphoma. Neoplastic cells were anaplastic and large, showing round, oval or irregularly shaped nuclei, prominent nucleoli and abundant

Fig. 1 **a** Initial skin lesions of our patient presenting with PC-ALCL. **b** Improvement of lesions after 4 cycles of CHOP regimen

cytoplasm. Immunohistochemically, tumor cells were positive for CD30, CD4, CD43 and CD45, and negative for EMA, ALK, CD3, CD5, CD7, CD8, CD20, CD45RO, CD56, TIA-1, perforin and granzyme B (Fig. 2). Thoracic and abdominal CT showed no lymphadenopathy or hepato splenomegaly.

After an 8-week period, the skin lesions did not show remission. On the contrary, their size increased. Furthermore, multiplicity of lesions, growing dimensions of the mass (7 × 2.5 cm), large size of tumors and former surgical removal accompanied by neoplastic relapse made us choose systemic chemotherapy. Thus, 4 cycles of cyclophosphamide (1200 mg/m^2), doxorubicin (60 mg/m^2), vincristine (2 mg) and prednisone (500 mg) were applied (CHOP regimen). There was immediate improvement of all lesions (Fig. 1b). The patient remains asymptomatic to date under close follow-up, 10 months after the last chemotherapy.

3 Discussion

In PC-ALCL, localized involvement in one anatomic region with multiple lesions occurs less frequently in comparison to localized involvement with one lesion [2]. Multifocal cutaneous disease is defined as the involvement of 2 or more anatomic areas [2] or an isolated lesional area exceeding 15 × 15 cm [3]. In this regard, skin lesions were localized rather than being multifocal. Several cases of CD30$^+$ PC-ALCL have been reported affecting among other sites, the skin of the eyelid and nose [4]. Patients with disseminated skin disease are prone to develop extracutaneous involvement and may benefit from systemic chemotherapy [5].

Systemic ALCL is characterized by infiltration of other organs and is generally more aggressive than PC-ALCL, the course of which is considered to be indolent (90% survival rate at 5 years) [2, 5]. Approximately, 20% of patients with systemic ALCL have skin involvement [6]. ALK expression in skin in majority of cases indicates systemic disease, because it is rare in PC-ALCL [6]. However, rare cases of ALK (+) PC-ALCLs have been described. Conversely, ALK negativity in skin does not exclude systemic disease. Reliable criteria are not currently available to distinguish PC-ALCL from systemic ALCL [ALK (−)] involving the skin. In addition, which of the cases of PC-ALCL are likely to disseminate to lymph nodes cannot be predicted. Like ALK, EMA expression is usually present in systemic ALCL with skin involvement, rather than in PC-ALCL [6, 7].

In our case, which was ALK (−) and EMA (−), secondary CD30$^+$ lymphoma due to mycosis fungoides (MF) was excluded, because of the absence of concurrent plaques with the characteristic histology of MF [3]. Despite our case being ALK (−), systemic ALCL [ALK (−)] involving skin did not seem to be the case, because of no involvement of lymph node sinuses or infiltration of internal organs, as proven by the negative findings of thoracic and abdominal CT, conducted for staging. Moreover, PC-ALCLs usually appear after 60 years of age, whereas there is predominance of young (<30 years) males with systemic ALCLs [2]. Immunohistochemical data against systemic ALCL in our case were lack of ALK and EMA expression [2]. Furthermore, LyP was excluded, because the lesions did not wax and wane, as LyP lesions do [5]. Moreover, spontaneous regression of the lesions was not noted. The diagnosis of PC-ALCL was therefore established. The absolute confirmation of our diagnosis can only be made after carefully monitoring our patient over time. Absence of ulcers in our patient is consistent with negativity of granzyme B and perforin, as frequent ulceration in PC-ALCL appears to be due to release of perforin and granzyme B from CD30$^+$ cells traced in skin lesions [2]. Although the head and extremities have been reported to be sites with predilection to PC-ALCL [5], there is lack of data in literature concerning the distribution of these rare neoplasms in particular anatomic sites of the upper or lower limbs. Careful staging, immunohistochemistry and

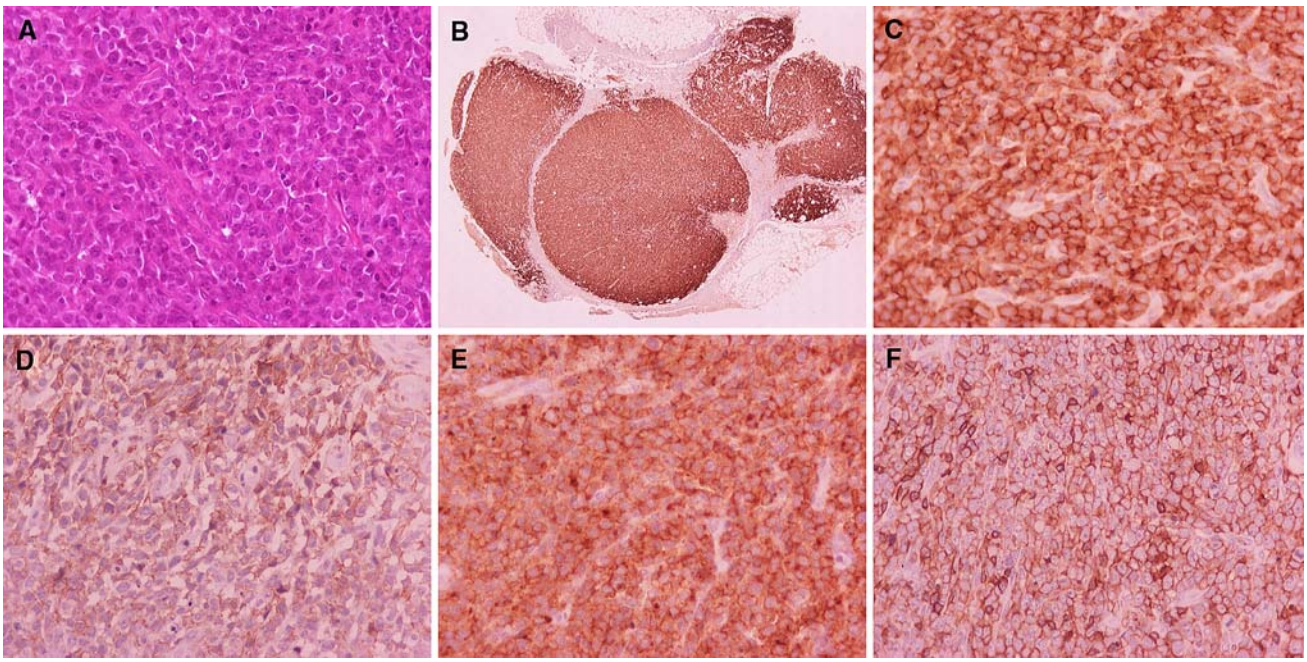

Fig. 2 **a** Infiltrate of large, anaplastic, atypical cells (hematoxylin and eosin stain, ×400). **b**, **c** Neoplastic cells are strongly positive for CD30/Ki. Immunohistochemical stainings ×20 (**b**), ×400 (**c**). **d** Tumor cells show positivity for CD45/LCA (×400). **e** Strong positivity for CD4 (×400). **f** CD43 positivity of neoplastic cells (×400)

close clinical follow-up remain the most reliable methods to confirm a PC-ALCL diagnosis.

Our treatment selection (CHOP) might be excessive to a degree. According to the recent guidelines from the International Peripheral T-Cell Lymphoma Project, multi-agent chemotherapy should be avoided, as it has not been associated with a better 5-year failure-free survival (FFS) or overall survival (OS), in comparison to radiotherapy or surgical excision or single-agent chemotherapy [1]. Although these recommendations were known since almost a decade [3], in a total of 22 recent patient series from America, Europe and Asia diagnosed with PC-ALCL, the majority of patients (13/22, 65%) received anthracycline-based multidrug chemotherapy, whereas 6 received radiotherapy alone, 2 had no further therapy and 1 had single-agent chemotherapy [1]. It seems that there is a tendency to over-estimate the hazards of PC-ALCL. In general, this cutaneous neoplasm, despite its fearsome name (anaplastic large cell lymphoma), has an indolent clinical course. However, exceptions exist. A case that is similar to ours has been reported, where a patient presenting with an enlarging PC-ALCL mass on his left femoral region was resistant even to multidrug chemotherapy (CHOP) [8]. In another case of PC-ALCL, 5 years after the initial diagnosis, an invasion of gastric mucosa, along with fatal leukemic progression was reported [9]. A new notion that has been recently described is that administration of cytotoxic drugs in patients with peripheral T-cell lymphomas, as in our case, might severely aggravate the already present immunodeficiency, causing EBV-associated lymphomas [10].

References

1. Savage KJ, Lee-Harris N, Vose JM, et al. International Peripheral T-Cell Lymphoma Project. ALK-negative anaplastic large-cell lymphoma (ALCL) is clinically and immunophenotypically different from both ALK-positive ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project. Blood. 2008;111:5496–504.
2. Droc C, Cualing HD, Kadin ME. Need for an improved molecular/genetic classification for $CD30^+$ lymphomas involving the skin. Cancer Control. 2007;14:124–32.
3. Bekkenk MW, Geelen FA, van Voorst Vader PC, et al. Primary and secondary cutaneous $CD30^+$ lymphoproliferative disorders: a report from the Dutch Cutaneous Lymphoma Group on the long-term follow-up data of 219 patients and guidelines for diagnosis and treatment. Blood. 2000;95:3653–61.
4. Martin JM, Ricart JM, Monteagudo C, et al. Primary cutaneous $CD30^+$ anaplastic large-cell lymphomas mimicking keratoacanthomas. Clin Exp Dermatol. 2007;32:668–71.
5. Kempf W. $CD30^+$ lymphoproliferative disorders: histopathology, differential diagnosis, new variants, and simulators. J Cutan Pathol. 2006;33(suppl 1):58–70.
6. Medeiros LJ, Elenitoba-Johnson KS. Anaplastic large cell lymphoma. Am J Clin Pathol. 2007;127:707–22.
7. Campo E, Chott A, Kinney MC, et al. Update on extranodal lymphomas: conclusions of the workshop held by the EAHP and

the SH in Thessaloniki, Greece. Histopathology. 2006;48:481–504.
8. Isogai R, Fukao M, Kawada A. Successful treatment for recurrence of primary cutaneous anaplastic large-cell lymphoma in elderly patient with etoposide, mitoxantrone, cyclophosphamide, vincristine, prednisolone and bleomycin (VNCOP-B) therapy. J Dermatol. 2007;34:556–60.
9. Tokura Y, Sugita K, Yagi H, et al. Primary cutaneous anaplastic large cell lymphoma with fatal leukemic outcome in association with CLA and CCR4-negative conversion. J Am Acad Dermatol. 2007;57(suppl 5):92–6.
10. Weisel KC, Weidmann E, Anagnostopoulos I, Kanz L, Pezzutto A, Subklewe M. Epstein–Barr virus-associated B-cell lymphoma secondary to FCD-C therapy in patients with peripheral T-cell lymphoma. Int J Hematol. 2008;88:434–40.