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Blastic plasmacytoid dendritic cell neoplasm: clinical features in 90 patients

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Summary

Background Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare disease characterized by malignant proliferation of a contingent blastic plasmacytoid dendritic cell. This rare entity is recognized mostly by cutaneous spreading, or not having a leukaemic component. The prognosis is very poor.

Objectives To study a large cohort of 90 patients with BPDCN, to define additional symptoms to form a correct diagnosis earlier, and to manage such patients accordingly.

Methods We retrospectively reviewed BPDCN cases registered in the French Study Group on Cutaneous Lymphoma database between November 1995 and January 2012. Ninety patients were studied. Demographic data, clinical presentation, initial staging and outcome were recorded.

Results The group contained 62 male and 28 female patients (sex ratio 2·2). Their ages ranged from 8 to 103 years at the time of diagnosis (mean 67·2 years). Three major different clinical presentations were identified. Sixty-six patients (73%) presented with nodular lesions only, 11 patients (12%) with 'bruise-like' patches and 13 (14%) with disseminated lesions (patches and nodules). Mucosal lesions were seen in five patients (6%). The median survival in patients with BPDCN was 12 months.

Conclusions We here distinguish three different clinical presentations of BPDCN. A nodular pattern is a more common feature than the originally reported 'bruise-like' pattern. Despite the fact that BPDCN may initially appear as a localized skin tumour, aggressive management including allogeneic bone marrow transplantation

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should be considered immediately, as it is currently the only option associated with long-term survival.

What's already known about this topic?

- Cutaneous spreading of blastic plasmacytoid dendritic cell neoplasm (BPDCN) has initially been reported as diffuse bruise-like macules.
- It may also present as an isolated tumoral nodule, a bruise-like macule, or an association of both.

What does this study add?

- This series of 90 patients with BPDCN helps to clarify the different clinical presentations.
- Three groups emerged from this study: the nodular form is the most frequent clinical subtype, bruise-like lesions represent a clinical pitfall, and disseminated lesions are the most suggestive clinical presentation. However, the clinical presentation is not a relevant prognosis factor.

Blastic plasmacytoid dendritic cell neoplasm (BPDCN), formerly known as CD4+CD56+ haematodermic neoplasm[1] or blastic natural-killer-cell lymphoma, is now defined in the 2008 World Health Organization classification of tumours of haematopoietic and lymphoid tissue as a rare disease characterized by malignant proliferation of a contingent blastic plasmacytoid dendritic cell.[2] It represents approximately 0·8% of primary cutaneous lymphomas.[3] BPDCN is the malignant counterpart derived from plasmacytoid dendritic cells (PDCs).[4–6] PDCs are characterized mainly by production of large amounts of interferon alpha.[7]

The phenotype is characterized by expression of CD4, CD56, CD123, blood dendritic cell antigen (BDCA)2, T-cell leukaemia/lymphoma (TCL)1 and B-cell chronic lymphocytic leukaemia/lymphoma (BCL)11A.[8] Although the diagnosis of BPDCN is most commonly made on the basis of cutaneous lesions, the leukaemic dissemination is constant during the natural progression of the disease.[5] This leukaemic dissemination may be present after, and even before, the initial skin diagnosis, or may appear during the weeks following the onset of cutaneous disease.[9,10] Although elderly people are the most commonly affected, congenital and paediatric cases have also rarely been reported.[11,12] The prognosis is poor and characterized by an aggressive clinical course. Although BPDCN is most often initially limited to the skin, only aggressive initial therapy has been shown to improve the overall prognosis. Currently, bone marrow (BM) transplantation is the only regimen allowing, although inconsistently, long-term survival.[13,14]

Cutaneous spreading of BPDCN has initially been reported as diffuse bruise-like macules. Beside this suggestive aspect, BPDCN may also present as an isolated tumoral nodule, a bruise-like macule, or concomitant tumoral and macular lesions. Herein, we report the results from a large cohort study of 90 patients with BPDCN and define additional clinical clues to suggest, as early as possible, the correct diagnosis to manage these patients accordingly.

Materials and methods

Patients registered in the French Study Group on Cutaneous Lymphoma (GFELC) database for BPDCN were retrospectively included. For each patient we obtained demographic data, previous medical history, age at onset of disease, first clinical symptoms, clinical pictures where available, staging at diagnosis, disease-free survival and overall survival. In all cases histological and phenotypic characteristics were in keeping with the diagnosis of BPDCN. While a few of these patients were previously reported in isolated case reports or included in pathology studies, 43 were included in a previous work from our group studying the different therapeutic options.[6,13,15–19]

After the regional pathologist and dermatologist/haematologist had first made the diagnosis, all of the cases were reviewed and discussed at GFELC meetings to be formally confirmed. Beside the routinely used CD3, CD4, CD8, CD20, CD56 and CD33 immunostaining, immunohistochemistry was completed by one of the authors (T.P.) using more specific antibodies looking for expression of CD123, TCL1, CD303 (BDCA2) and BCL11A before the case was definitively registered as BPDCN. Clinical description and, where available, anonymized clinical pictures were reviewed. Initial staging included clinical examination, BM biopsy, chest–abdominal and pelvis computerized tomography (CT) scan, and blood sample microscopy. Blood involvement was initially defined by the presence of a contingent of large circulating CD4+ CD56+ cells by cytometry. CD123, BDCA2 and BDCA4 have now been added to the panel of antibodies tested in flow cytometry, but were not available when the first patients were

tested. Statistical analysis was performed using the SPSS 19.0® software (SPSS Inc., Chicago, IL, U.S.A.).

This study has not been registered in a public trial registry because it is not a project that 'prospectively assigns human subjects to intervention or comparison groups to evaluate the cause and effect relationship between a medical intervention and a health outcome'.

Results

Ninety patients were registered as having BPDCN in the GFELC database between November 1995 and January 2012. The clinical data of the patients are summarized in Table 1.

The study group contained 62 male and 28 female patients (sex ratio 2·2), whose ages ranged from 8 to 103 years at the time of diagnosis (mean 67·2 years). Two children (2%) were included in the study.

Clinical history included previous myeloproliferative disorders in 10 patients: chronic myeloid leukaemia (six patients, nos 38, 48, 57, 65, 74, 88); myelodysplastic syndrome (three patients, nos 55, 78, 79); myeloma (one patient, no. 85); and essential thrombocythaemia (one patient, no. 57).

The skin lesions appeared as brownish to violaceous infiltrated 'bruise-like' patches, plaques or tumours. Clinical presentation varied widely, from one or two skin nodules or tumour to disseminated cutaneous spread. Three major groups of clinical patterns were observed.

Group 1 included 66 patients (73%) presenting with nodular lesions only (Fig. 1). Group 2 included 11 patients (12%) showing 'bruise-like' patches (Figs 2 and 3). Group 3 contained the 13 remaining cases (14%), presenting disseminated and mixed lesions (macules and nodules; Fig. 4). Forty-two patients (47%) presented initially with localized nodular disease defined as one or two isolated cutaneous nodules. The face or scalp was primarily affected in 18 cases, while the lower limb, trunk and upper limb were affected in 10, eight and six cases, respectively. Twenty-four patients (27%) presented with multiple nodules affecting one or two areas, especially the trunk (18), limb (three) and head (three).

Eleven patients (12%) presented bruise-like patches. Only two of these patients (18%) had a single lesion (lower limb and head), whereas nine (82%) had several lesions limited to one or two body areas (trunk, eight; lower limb, one). Mucosal involvement was noticed in five patients (6%; nos 21, 29, 70, 85, 86) (Figs 5 and 6).

Complete staging investigations included blood examination (smear samples and flow cytometry analysis), BM biopsy and CT scan of the chest/abdomen and pelvis. Results of the initial staging investigations were not available for seven patients. Two of them died before staging was completed, and two refused the BM aspiration, which was not ethically appropriate in the last case. Initial staging was negative in 28 of 83 patients (34%), while 55 (66%) had BM, lymph node and/or blood involvement. Among the 59 patients with cutaneous nodules 36% had a negative initial staging. Furthermore, four of the 11 patients (36%) with bruise-like patches had a negative initial staging. Only two of 13 patients (15%) with generalized lesions had a negative initial staging.

Nine patients (11%), had central nervous system damage (patients 11, 20, 25, 38, 47, 49, 70, 86, 87), mainly neuromeningeal involvement. Although lumbar puncture and brain CT were not routinely performed, this central nervous system involvement was diagnosed following clinical symptoms including meningeal signs, confusion and seizure.

The mean survival of patients with BPDCN was 15·3 months (95% confidence interval 12·7–17·9). Only 14 patients (16%) were still alive when the study was performed (survival ranged from 6 months to 6 years). There was no statistically significant difference between the different clinical presentations. The mean survival was 15·5, 14·2 and 15·1 months, respectively, in groups 1, 2 and 3 ($P = 0·9$; Fig. 7). The overall survival did not significantly correlate with the results of the initial staging ($P = 0·35$; Fig. 8)

The mean time between the onset of lesions and the final diagnosis was 6·2 months (Table 2). This delay has decreased over the last 15 years, probably due to increased knowledge of the disease by both clinicians and pathologists.

Discussion

BPDCN is a serious disease. To the best of our knowledge BM transplantation represents the best chance to obtain long-term remission.[13] Early clinical and pathological diagnosis, allowing a BM transplant, is thus crucial to reach complete biological remission.

The original cutaneous description of BPDCN was performed in our group.[6] Since then, more than 100 cases bearing diagnostic criteria for BPDCN have been reported in the English literature. BPDCN predominantly affects men (sex ratio 2·2) and the elderly, with patients in this study having an average age of 67·2 years (range 8–103 years), similar to that found in the literature.[3,9,11,13,20,21] The initial reports generally pointed out the bruise-like clinical form of BPDCN.

In this study we actually observed three major presentation features: (i) one or few isolated purplish nodules; (ii) one or few purplish bruise-like macules; and (iii) disseminated lesions (macules and nodules).

Purplish nodules (Fig. 1) are, in our experience, the most common presentation of BPDCN, and present in up to 73% of cases (47% of patients with one or two nodules and 27% with more than two nodules). This presentation in our series is more frequent than previously reported by Cota *et al.*[9] (73% vs. 36%), although that study included only 33 patients. Table 3 compares the two studies. Isolated nodules (one or two) were more commonly located on the head or lower limbs, while multiple nodules affected mainly the trunk. Their larger diameter ranged from 5 mm to > 100 mm.

Localized purplish macules (bruise-like lesions) as a unique cutaneous finding were a less common feature (12%), but were insidious and often considered to be trauma-induced bruises (Figs 2 and 3). However, considering the macular pattern, macules are usually multiple (82%) and less

Table 1 Patient characteristics: clinical data, initial staging and outcome

Patient no.	Sex/age (years)	Clinical presentation	Body site	Staging	Follow-up
1	F/86	Two nodules	Lower limb	BM−, LN+, blood−	DCD 5 months
2	F/67	Several nodules/plaques	Trunk	BM−, LN−, blood−	DCD 17 months
3	M/84	Several nodules	Head	BM+, LN+, blood−	DCD 5 months
4	F/65	One nodule	Lower limb	BM−, LN+, blood−	DCD 17 months
5	F/49	One nodule	Head	BM−, LN+, blood−	DCD 9 months
6	M/37	One nodule	Lower limb	BM−, LN−, blood−	DCD 40 months
7	M/8	One bruise-like tumefaction	Lower limb	BM−, LN+, blood−	DCD 33 months
8	M/62	Several bruise-like tumefactions	Trunk	BM−, LN−, blood−	DCD 13 months
9	M/72	One nodule	Upper limb	BM+, LN+, blood+	DCD 3 months
10	F/33	One nodule	Lower limb	BM−, LN+, blood−	DCD 27 months
11	M/77	Several nodules	Trunk	BM−, LN−, blood−	DCD 12 months
12	M/64	Several bruise-like tumefactions	Trunk	BM+, LN−, blood−	DCD 12 months
13	F/88	Disseminated nodules	Generalized	BM−, LN−, blood−	DCD 8 months
14	M/69	Disseminated nodules	Generalized	BM−, LN−, blood−	DCD 21 months
15	M/82	One nodule	Head	BM−, LN−, blood−	DCD 24 months
16	M/69	Several nodules	Trunk	Unknown	DCD 2 months
17	M/75	Several nodules	Trunk	BM−, LN+, blood−	DCD 26 months
18	M/81	Several bruise-like tumefactions	Trunk	BM−, LN−, blood−	DCD 11 months
19	M/56	Disseminated nodules	Generalized	BM+, LN+, blood+	DCD 13 months
20	F/54	Several nodules	Lower limb	BM−, LN−, blood−	DCD 7 months
21	M/72	Several nodules	Trunk	BM+, LN+, blood+	DCD 10 months
22	M/70	One nodule	Head	BM−, LN−, blood−	DCD 19 months
23	F/96	One nodule	Head	BM−, LN+, blood−	DCD 1 month
24	F/70	One nodule	Upper limb	BM+, LN−, blood−	DCD 24 months
25	M/73	One nodule	Upper limb	BM−, LN−, blood−	DCD 20 months
26	F/63	One nodule	Head	BM−, LN−, blood−	DCD 24 months
27	M/64	One nodule	Head	Unknown	Unknown
28	F/81	Two nodules	Trunk, lower limb	BM−, LN−, blood−	DCD 8 months
29	M/75	One nodule	Upper limb	BM−, LN−, blood−	DCD 11 months
30	F/60	One nodule	Head	BM−, LN−, blood−	PR 11 months/LFU
31	M/63	Several nodules	Trunk, upper limb	BM−, LN−, blood−	DCD 15 months
32	M/25	Disseminated nodules	Generalized	BM+, LN+, blood+	DCD 19 months
33	M/83	One nodule	Head	BM−, LN−, blood−	LFU
34	M/68	One nodule	Trunk	BM+, LN+, blood−	DCD 48 months
35	F/35	One nodule	Lower limb	BM−, LN−, blood−	Alive at 72 months
36	M/76	Several nodules	Trunk	BM+, LN+, blood−	DCD 7 months
37	M/71	Two nodules	Lower limb	BM−, LN−, blood−	DCD 9 months
38	M/60	One nodule	Trunk	BM−, LN−, blood−	DCD 12 months
39	M/82	Disseminated nodules	Generalized	BM+, LN+, blood+	DCD 9 months
40	F/42	One nodule	Lower limb	Unknown	Unknown
41	M/80	Disseminated nodules	Generalized	BM+, LN−, blood+	DCD 3 months
42	F/82	One nodule	Lower limb	BM−, LN−, blood−	DCD 18 months
43	F/77	Several nodules	Upper limb	BM−, LN+, blood−	DCD 5 months
44	M/35	Several nodules	Trunk, head	BM+, LN+, blood+	CR 16 months/LFU
45	F/70	One nodule	Upper limb	Unknown	Unknown
46	M/84	Several bruise-like tumefactions	Trunk	BM+, LN+, blood−	DCD 3 months
47	M/70	One nodule	Head	BM+, LN−, blood−	DCD 13 months
48	M/75	Several nodules	Trunk	Unknown	Unknown
49	M/83	Two nodules	Head, trunk	BM+, LN+, blood−	DCD 6 months
50	M/35	Two nodules	Head, trunk	BM+, LN+, blood+	DCD 18 months
51	M/78	Several nodules	Lower limb	BM−, LN+, blood−	DCD 8 months
52	M/38	Disseminated nodules	Generalized	BM+, LN+, blood+	DCD 18 months
53	F/69	Disseminated nodules	Generalized	BM+, LN−, blood−	DCD 7 months
54	F/86	Several bruise-like tumefactions	Trunk, upper limb	BM+, LN−, blood+	DCD 12 months
55	M/68	Several nodules	Trunk	BM−, LN−, blood−	DCD 18 months
56	M/65	Several bruise-like tumefactions	Trunk	BM−, LN−, blood−	DCD 9 months
57	M/70	Disseminated nodules	Generalized	BM+, LN+, blood+	Alive at 36 months
58	M/58	One nodule	Lower limb	BM−, LN−, blood+	DCD 10 months
59	F/29	One nodule	Lower limb	BM−, LN+, blood−	Alive at 36 months

Table 1 (continued)

Patient no.	Sex/age (years)	Clinical presentation	Body site	Staging	Follow-up
60	M/80	Several nodules	Trunk	BM−, LN+, blood−	DCD 15 months
61	M/79	One nodule	Head	BM−, LN−, blood−	Unknown
62	M/79	One nodule	Head	BM+, LN−, blood−	DCD 5 months
63	M/42	One nodule	Trunk	BM+, LN−, blood−	Alive at 36 months
64	F/63	One nodule	Head	BM−, LN−, blood−	Alive at 36 months
65	M/70	Two nodules	Trunk	BM−, LN−, blood+	DCD 9 months
66	M/61	Two nodules	Trunk	BM+, LN−, blood−	DCD 24 months
67	F/71	Three nodules and bruise-like tumefactions	Head, trunk	BM−, LN−, blood+	DCD 1 month
68	M/80	Disseminated bruise-like tumefactions	Generalized	BM+, LN+, blood−	DCD 10 months
69	M/70	Three bruise-like tumefactions	Trunk	BM−, LN+, blood+	DCD 9 months
70	M/57	Two bruise-like tumefactions	Head, lower limb	BM+, LN+, blood+	DCD 28 months
71	F/76	Three nodules	Trunk, head	BM+, LN−, blood−	Alive at 24 months
72	M/103	Four nodules	Trunk, head	Unknown	DCD 6 months
73	M/82	One nodule	Upper limb	BM+, LN−, blood+	DCD 16 months
74	M/67	Two nodules	Head	BM−, LN+, blood−	DCD 14 months
75	M/73	Five nodules	Trunk, upper limb	BM+, LN+, blood+	DCD 12 months
76	F/88	One nodule	Head	BM−, LN+, blood−	Alive at 12 months
77	F/65	One nodule	Trunk	BM+, LN+, blood−	DCD 7 months
78	F/78	Several nodules	Trunk	BM−, LN−, blood+	Unknown
79	M/82	One nodule	Head	Unknown	Unknown
80	M/29	Two nodules	Head	BM−, LN−, blood−	Alive at 4 months
81	F/88	Several nodules	Trunk	BM−, LN−, blood−	Alive at 6 months
82	M/81	Several nodules	Trunk	BM−, LN−, blood+	DCD 1 month
83	M/93	Disseminated nodules	Generalized	BM−, LN+, blood−	DCD 24 months
84	M/74	Disseminated nodules	Generalized	BM+, LN−, blood+	DCD 11 months
85	M/62	Disseminated bruise-like tumefactions	Generalized	BM+, LN+, blood−	Alive at 17 months
86	M/84	Several bruise-like tumefactions	Trunk	BM−, LN+, blood−	Alive at 8 months
87	M/69	Several nodules	Trunk, head	BM+, LN−, blood−	Alive at 20 months
88	M/50	Two nodules	Trunk	BM+, LN+, blood−	Alive at 6 months
89	M/82	Several nodules	Trunk	BM+, LN+, blood+	LFU
90	F/9	Three bruise-like tumefactions	Head, limb	BM−, LN−, blood−	Alive at 18 months

LFU, lost to follow-up; BM, bone marrow; LN, lymph node; DCD, deceased; PR, partial response; CR, complete response.

commonly isolated (18%). Similar results were found by Cota *et al.*[9] (Table 3).

Disseminated cutaneous lesions (Fig. 4) are indeed uncommon, representing only 15% of cases, but for clinicians this was the most suggestive clinical presentation. They are characterized by the association of nodules, papules and purpuric generalized macules. Although we can hypothesize that localized forms (group 1) may evolve to a more diffuse disease (group 3), from our observations it is more likely that patients in group 1 may experience only a limited skin disease, while those in group 3 present a diffuse skin disease from the very beginning. Moreover, leukaemic dissemination might occur irrespective of the cutaneous spreading. Mucosal involvement (Figs 5 and 6) was reported in five patients (6%), especially in oral mucosa. So far it has rarely been described in the literature. Two cases with pharynx involvement have been reported by Hashikawa *et al.*[22] However, we can speculate that this spreading is underdiagnosed.

In our series, two children (2%) were affected (nos 7 and 90). They both had cutaneous involvement with bruise-like lesions. In a retrospective study of BPDCN in a paediatric population it was shown that cutaneous findings were absent in up to 24% of cases.[11] In contrast to the poor prognosis observed in adults, BPDCN is supposed to be associated with a relatively more favourable outcome in children, and is associated with a significant response to intensive acute lymphoblastic leukaemia-type chemotherapy.[11,22] However, larger series are needed to confirm this hypothesis. The congenital form seems exceptional, with only one case reported.[12]

We observed central nervous system involvement in nine patients (10%); this is in keeping with previous studies where the incidence ranged from 9% to 26%.[23–25] The central nervous system may represent a persistent BPDCN blast sanctuary.[5] These data are crucial to determine the best therapeutic option. To this end, intrathecal chemoprophylaxis should possibly be considered.[5,25] The prognosis of the disease is often fatal, with a survival of a few months.[3,9,11,13,21] The median survival was 12 months in our study.

In our cohort, due to recruitment bias through using a dermatological group, cutaneous spreading was constant. According to the literature, almost 85% of cases of BPDCN show cutaneous involvement at presentation.[26,27]

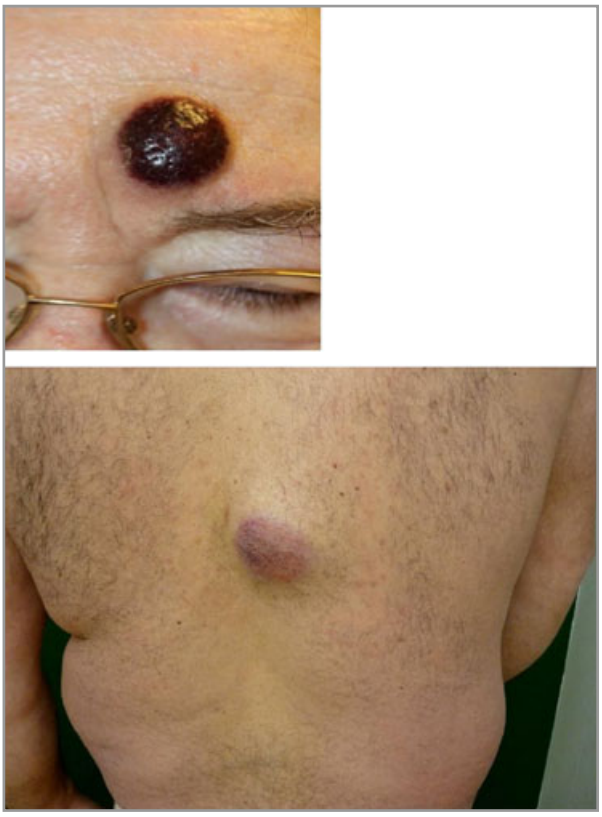

Fig 1. Nodular lesions, patients 71 and 63.

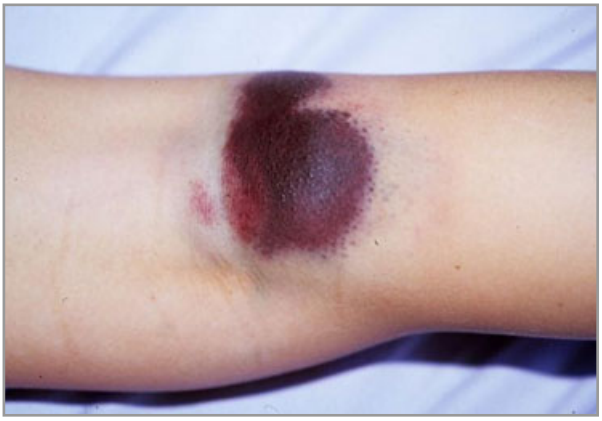

Fig 2. 'Bruise-like' lesion, patient 7.

BPDCN is an aggressive disease, and so far BM transplantation should be considered the first therapeutic option, at least in the disseminated stage of the disease. Recently, Roos-Weil *et al.*[28] provided evidence that high-dose therapy followed by allo-stem cell transplantation from related and unrelated donors can provide durable disease control in up to 50% of patients. The best therapeutic option when only the skin is affected is still a matter of debate and needs further evidence.

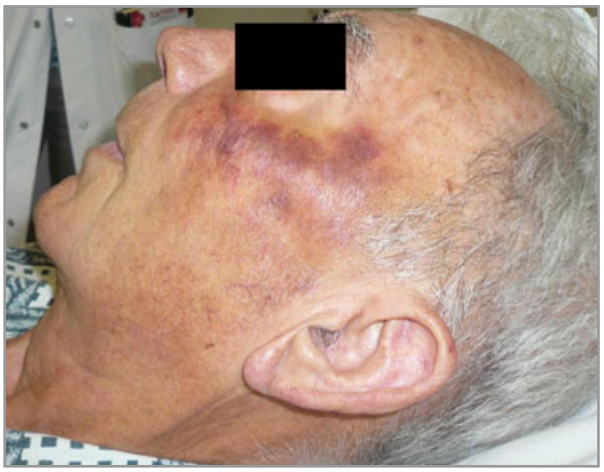

Fig 3. 'Bruise-like' lesions, patient 68.

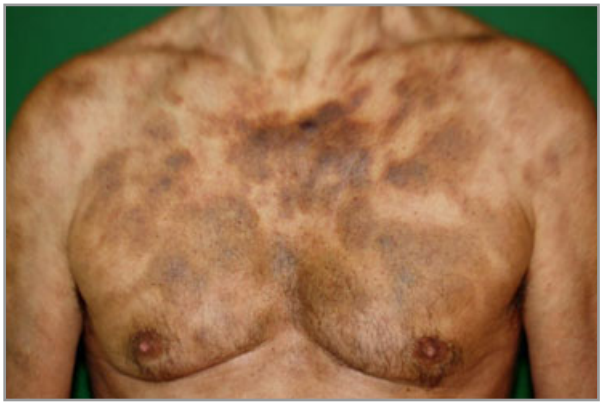

Fig 4. Disseminated lesions, patient 85.

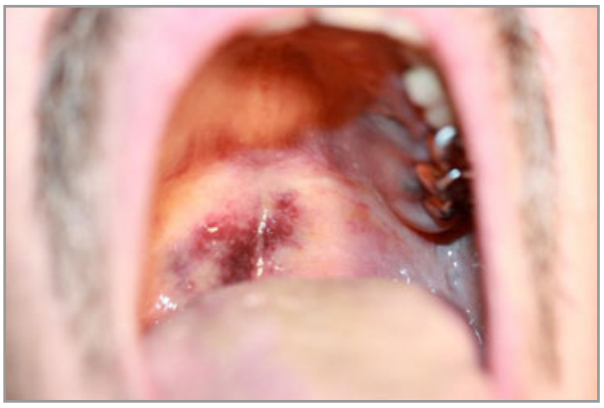

Fig 5. Mucosal lesion in patient 85.

In this series, we aimed to correlate the clinical presentation with prognosis. However, even though the outcome seemed more favourable in patients with nodular lesions, based on a Kaplan–Meier curve (Fig. 7) no difference was observed between the three populations ($P = 0{\cdot}9$). Clinical presentation is not currently a significant prognostic factor.

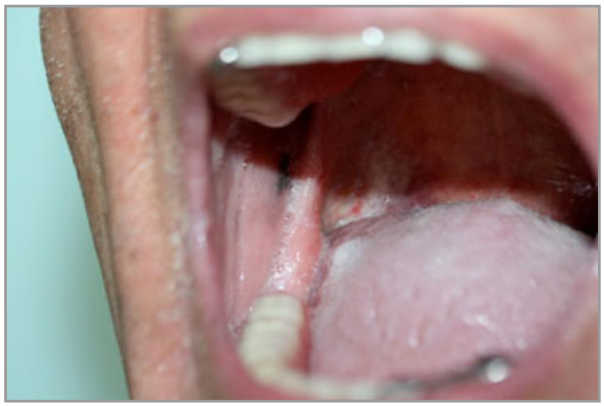

Fig 6. Mucosal lesion in patient 86.

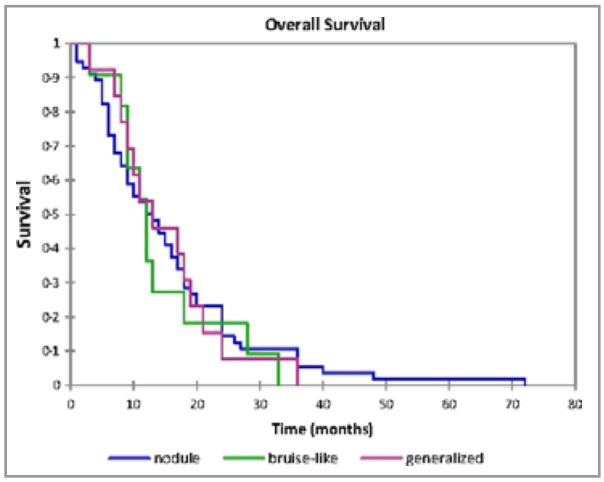

Fig 7. Kaplan–Meier survival analysis related to clinical presentation.

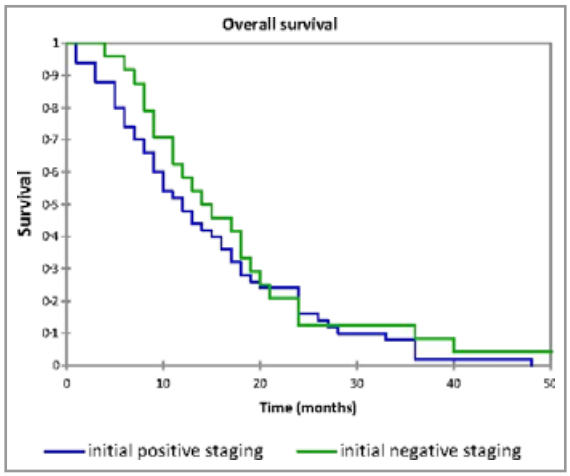

Fig 8. Kaplan–Meier survival analysis related to the initial staging.

Beyond clinical presentation, genetic[26] and molecular studies[8] have been performed by other groups to identify relevant prognostic criteria. Chemokine receptors, which mediate the migration of lymphocytes through binding of their ligands, have been investigated. These receptors play a critical role in tumour initiation, promotion and progression. Chemokine (C-X-C motif) ligand (CXCL)12, for example, enhances migration of follicular lymphoma cells, and the circuitry of CXCL12 and CXCR4 (a CXCL12 receptor) appears to be crucial for migration of chronic lymphocytic leukaemia and acute lymphoblastic leukaemia B cells. CXCL12 may be associated with the migration of blastic PDCs through pseudopodia formation and leukaemic changes.[22] This study of 26 patients showed that high CXCL12 expression in BPDCN is associated with systemic dissemination and poor prognosis. The CXCR4–CXCL12 circuitry might then be an interesting target for BPDCN management.[22]

Jaye *et al.*[29] found an inverse correlation between expression of terminal deoxynucleotidyl transferase (TdT) and BDCA2, and postulated that TdT+/BDCA2− cells correspond to earlier PDC precursors, whereas TdT−/BDCA2+ cells correspond to more differentiated PDCs. BDCA2+ cases were associated with reduced survival compared with BDCA2− patients. Furthermore, high TdT expression in cases from a series reported by Bekkenk *et al.*,[30] where the disease had been called blastic

Table 2 Mean delay between the onset of lesions and final diagnosis

Year	Patients	Delay (months)
1995	1	12
1996	1	18
2001	4	4·5
2003	3	2·6
2004	1	12
2005	2	5·5
2006	2	2
2007	4	4
2008	6	2·6
2009	9	4·6
2010	5	2·95
2011	5	4·4

Table 3 Comparison of our data with the study of Cota *et al.*[9]

	This study	Cota *et al.*
Number of patients	90	33
Sex ratio	2·2 (62 M/28 F)	7·25 (29 M/4 F)
Mean age (years)	67·2	71
Age range (years)	8–103	30–89
Clinical features, n (%)		
Generalized lesions	13 (14)	18 (55)
Nodular lesions	66 (73)	12 (36)
Bruise-like lesions	11 (12)	3 (9)
Initial staging, n (%)		
Negative	28 (31)	20 (61)
Positive	55 (61)	9 (27)
Unknown	7 (8)	4 (12)

M, male; F, female.

natural-killer-cell lymphoma, was associated with a more favourable prognosis. An additional study is currently ongoing in our group to investigate these and additional specific antigens.

Cytogenetic investigations have shown the predominance of genomic losses affecting 5q21 or 5q34 (72%), 12p13 (64%), 13q13–q21 (64%), 6q23–qter (50%), 15q (43%) and all of chromosome 9 (28%).[26,31] More recently, a study showed loss of the cell-cycle genes *CDKN1B*, *CDKN2A* and *TP53*.[31] In this latter study of 21 cases it was suggested that mutation of *CDKN2A/CDKN2B* on chromosome 9 could help to identify the most aggressive cases; however, the results could not be shown to be significant in that small cohort.[31]

In conclusion, this series of 90 cases of BPDCN helps to clarify the different clinical presentations of the disease. Three groups emerged from this study. The nodular form is the most frequent clinical subtype. The bruise-like lesions represent a clinical pitfall, while the disseminated lesions are the most suggestive clinical presentation. However, the clinical presentation is not a relevant prognosis factor. Only an aggressive initial therapy, even for localized disease, may improve the overall prognosis. Several genetic, molecular and immunohistochemical studies are ongoing to identify additional prognosis criteria and specific targets to optimize the therapeutic management of this disease.

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