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Pityriasis lichenoides et varioliformis acuta with numerous CD30(+) cells: a variant mimicking lymphomatoid papulosis and other cutaneous lymphomas. A clinicopathologic, immunohistochemical, and molecular biological study of 13 cases

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Pityriasis lichenoides et varioliformis acuta with numerous CD30+ cells: a variant mimicking lymphomatoid papulosis and other cutaneous lymphomas. A clinicopathological, immunohistochemical and molecular biological study of 13 cases. --Manuscript Draft--

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Abstract:	<p>Pityriasis lichenoides comprises a clinicopathological spectrum of cutaneous inflammatory disorders, with the two most common variants, pityriasis lichenoides et varioliformis acuta (PLEVA) and pityriasis lichenoides chronica. The aim of the study is to describe 13 cases of a unique PLEVA variant characterized with a conspicuous CD30+ component and thus mimicking lymphomatoid papulosis (LyP), a condition currently classified with a spectrum of CD30+ lymphoproliferative disorders. The cohort included 10 female and 3 male patients whose age at diagnosis ranged from 7 to 89 years (mean 41 years; median 39 years). The clinical manifestation was that of PLEVA, with small erythematous macules quickly evolving into necrotic papules. There was no waxing and waning course on follow-up in any of the cases.</p> <p>Histopathologically, typical features of PLEVA were present but an unusual finding was occurrence of a considerable number of CD30+ small lymphocytes as detected immunohistochemically. Over half of the cases also displayed a high number of CD8-positive cells and showed co-expression of CD8 and CD30 in the intraepidermal and dermal component of the infiltrate. Of the 11 cases of PLEVA studied for TCR gene rearrangement, 6 evidenced a monoclonal T-cell population and 5 were polyclonal. Parvovirus B19 (PVB19) DNA was identified in 4 of 10 cases investigated and positive serology for PVB19 in two patients, altogether suggesting that PVB19 is pathogenetically linked to PLEVA at least in a subset of cases. The presence of CD30-positive lymphocytes and CD8-positive lymphocytes would be consistent with an inflammatory antiviral response, since CD30-positive, even atypically appearing lymphoid cells have been identified in some viral skin diseases. The main significance</p>

of the PLEVA variant is however its potential confusion with LyP or some cytotoxic lymphomas. Admittedly, the CD30+ PLEVA variant described herein and LyP show a great overlap if one takes into account all known variations of the two conditions recognized in recent years, thus suggesting that LyP and PLEVA may be much more biologically closely related entities than currently thought or even can occur on a clinicopathological spectrum.

Manuscript revision. AJSP-D-12-00017, entitled "Pityriasis lichenoides et varioliformis acuta with numerous CD30+ cells: a variant mimicking lymphomatoid papulosis and other cutaneous lymphomas. A clinicopathological, immunohistochemical and molecular biological study of 13 cases."

February 6, 2012

Dear Dr Mills,

Enclosed please find the revised version of our manuscript. Following your kind suggestion to make composite figures and thus reduce the cost of color production, please note that we have now added 2 composite figures in the revised version instead of separate parts (Figures 3,4).

We have also added one reference (Ref. 8) – this paper has just been published and we feel this reference would be relevant as it further supports some of our ideas in the Discussion.

These are the only changes made in the revised version. Enclosed please also find our replies to the referees' comments. We thank you and both reviewers for your time and consideration.

Sincerely yours,

Werner Kempf, MD

Replies to reviewers

Reviewer #1:

This is a careful study of what appears to be a subgroup of pityriasis lichenoides, with CD30 positive cells and co-expression of CD8. The authors make a convincing case that this is a different disorder from lymphomatoid papulosis, but also suggest that these may all be closely related diseases. The association with parvovirus B19 is also interesting, supporting the previous study by Tomasini and the long-held suspicions by clinicians that PLEVA may be virally-induced. Further, this group of disorders could represent a family of T-cell dyscrasias induced by parvovirus or other infectious or non-infectious agents.

Our reply:

We thank the reviewer for his/her time and high evaluation of our manuscript. With respect of the hypothesis that the entities we report on might represent a family of T-cell dyscrasias, please note that we did mention this in the original version and have now highlighted red this sentence in the revised version.

Reviewer #2:

The manuscript Pityriasis lichenoides et varioliformis acuta with numerous CD30+ cells: a variant mimicking lymphomatoid papulosis and other cutaneous lymphomas. A clinicopathological, immunohistochemical and molecular biological study of 13 cases is a description of 13 cases of PLEVA and PLC with an unusual component of CD30+ cells mimicking lymphomatoid papulosis using H and E stains, immunochemistry and polymerase chain reaction. The authors study these cases for Parvovirus 19 and detect its presence in 40% of cases, confirming a single prior study. The authors contrast the clinicopathologic features of these entities.

This paper is well written and precise with excellent photographic representation and extensive up to date refernces. It describes a dilemma that dermatopathologists face and offers sound criteria. Although much of this information has been reported, this paper discusses the overlaps that often occur in the laboratory setting rather than the neat demarcations described in textbooks.

Our reply:

We thank the referee for his/her time and high evaluation of our manuscript.

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2 **mimicking lymphomatoid papulosis and other cutaneous lymphomas. A**
3 **clinicopathological, immunohistochemical and molecular biological study of 13 cases.**
4

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6 Freitag (5), Leo Schaerer (4), Heinz Kutzner (4)
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Running title: CD30+ PLEVA

Key words: CD30, pityriasis lichenoides, clonality, parvovirus B19

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Abstract

1 Pityriasis lichenoides comprises a clinicopathological spectrum of cutaneous inflammatory
2 disorders, with the two most common variants, pityriasis lichenoides et varioliformis acuta
3 (PLEVA) and pityriasis lichenoides chronica. The aim of the study is to describe 13 cases of a
4 unique PLEVA variant characterized with a conspicuous CD30+ component and thus
5 mimicking lymphomatoid papulosis (LyP), a condition currently classified with a spectrum of
6 CD30+ lymphoproliferative disorders. The cohort included 10 female and 3 male patients
7 whose age at diagnosis ranged from 7 to 89 years (mean 41 years; median 39 years). The
8 clinical manifestation was that of PLEVA, with small erythematous macules quickly evolving
9 into necrotic papules. There was no waxing and waning course on follow-up in any of the
10 cases. Histopathologically, typical features of PLEVA were present but an unusual finding
11 was occurrence of a considerable number of CD30+ small lymphocytes as detected
12 immunohistochemically. Over half of the cases also displayed a high number of CD8-positive
13 cells and showed co-expression of CD8 and CD30 in the intraepidermal and dermal
14 component of the infiltrate. Of the 11 cases of PLEVA studied for TCR gene rearrangement, 6
15 evidenced a monoclonal T-cell population and 5 were polyclonal. Parvovirus B19 (PVB19)
16 DNA was identified in 4 of 10 cases investigated and positive serology for PVB19 in two
17 patients, altogether suggesting that PVB19 is pathogenetically linked to PLEVA at least in a
18 subset of cases. The presence of CD30-positive lymphocytes and CD8-positive lymphocytes
19 would be consistent with an inflammatory antiviral response, since CD30-positive, even
20 atypically appearing lymphoid cells have been identified in some viral skin diseases. The
21 main significance of the PLEVA variant is however its potential confusion with LyP or some
22 cytotoxic lymphomas. Admittedly, the CD30+ PLEVA variant described herein and LyP
23 show a great overlap if one takes into account all known variations of the two conditions
24 recognized in recent years, thus suggesting that LyP and PLEVA may be much more
25 biologically closely related entities than currently thought or even can occur on a
26 clinicopathological spectrum.
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39 Key words cutaneous lymphoma, CD30, lymphomatoid papulosis, pityriasis lichenoides,
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Introduction

Pityriasis lichenoides comprises a clinicopathological spectrum of cutaneous inflammatory disorders, of which the two most common variants, pityriasis lichenoides et varioliformis acuta (PLEVA) or Mucha–Habermann disease and pityriasis lichenoides chronica are usually considered to represent the polar ends, with well-documented intermediate or overlapping forms, including concurrent and sequential occurrence of PLEVA and pityriasis lichenoides chronica in the same patient. (11), (41), (52) Whereas PLEVA is clinically characterized by erythematous papules that rapidly become vesicular and hemorrhagic and finally necrotic and ulcerative, pityriasis lichenoides chronica manifests a more monomorphous eruption of lichenoid brownish-red, mica-like scaling papules. Compared with adults, childhood pityriasis lichenoides has been shown to often run a long-standing and occasionally unremitting course, with greater distribution of the lesions, more dyspigmentation, seasonal variation and a poorer response to conventional treatment modalities. (23), (28), (58), (71) A less common but apparently distinct variation is febrile ulceronecrotic Mucha-Habermann disease characterized by a rapid progression of necrotic papules to large coalescent ulcers with necrotic crusts, pustules or hemorrhagic bullae variably accompanied by systemic manifestations (high fever, abdominal pain, diarrhea, central nervous system symptoms) and laboratory changes (leukocytosis, increased levels of C-protein, anemia etc). Involvement of oral and genital mucosa may be encountered and a few fatal cases of febrile ulceronecrotic PLEVA have been documented. (17), (18), (25), (56), (63), (67), (68)

Similar to the clinical overlap there is also overlap in the histopathological presentation of the above mentioned disease variants. The common features include parakeratosis, spongiosis with occasional spongiotic vesicles, mild to moderate acanthosis, vacuolar alteration at the dermoepidermal junction, necrotic keratinocytes, lymphocytic perivascular inflammatory infiltrate which is often wedge-shaped and obscures the dermoepidermal junction, with variable extension into the deeper reticular dermis, and erythrocyte extravasation. Angiocentric infiltrates and vasculitic changes can also be encountered on occasion. It is the degree of keratinocyte necrosis, erythrocyte extravasation, density of the infiltrate, involvement of the deep dermal vascular plexus and presence/severity of vasculitis that vary in the clinical forms of pityriasis lichenoides. (7), (35), (48), (57)

Immunohistochemically, the lymphocytic population in PLEVA is mostly represented by cytotoxic T cells with the predominance of a memory T-cell subpopulation (CD45RO+, CD2+, CD3+, CD8+, TIA-1+, Granzym B–). (29), (36), (65), (75) Subtle variation of the immunophenotype of the cells between the intraepidermal and intradermal components can be observed. Also, a slight variation in the immunoprofile between individual cases has been reported, as has differences in immunoprofile from different lesions from the same patient. A handful of cases of PLEVA have been reported in which scattered lymphoid cells expressed CD30, (34), (53). Some authors (59) however suggested that these might have in fact represented lymphomatoid papulosis (LyP), a condition currently classified in the spectrum of the primary cutaneous CD30+lymphoproliferative disorders. (20), (1), (12), (39), (55), (77)

In recent years, we have encountered several unusual cases of PLEVA with a conspicuous CD30 +component that warranted, at least from histopathological prospective, a differential

1 diagnostic consideration of LyP. However, in contrast to LyP, which is characterized by a
2 chronic, recurrent, self-healing papular eruption with a typical a waxing and waning course,
3 these clinical features were not observed in any of the CD30+ PLEVA cases. The aim of the
4 study is to describe 13 cases of this unique PLEVA variant, including molecular biological
5 investigations for T-cell clonality and parvovirus B19 (PVB19), and to emphasize its
6 differentiation from LyP and other cutaneous lymphomas. The rationale for studying PVB19
7 was the conclusions of a recent study on PLEVA in which the authors suggested a causal role
8 of the virus in this condition. (65) We sought to see whether the same can be documented for
9 the PLEVA variant we describe herewith and also studied 20 classic cases of LyP for PVB19
10 for comparison.
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14 **Material and Methods**

15 Inclusion/exclusion criteria

16 The inclusion criteria were:

- 17 1) clinical appearances compatible with PLEVA supported by histopathological features
18 typical for the disease,
- 19 2) lack of waxing and an and waning of the lesions as typical for LyP, and
- 20 3) presence in the infiltrate of a considerable number of small (or sometimes medium-sized)
21 CD30+ lymphocytes as detected immunohistochemically.
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28 Excluded were cases in which there was at least a single *large* CD30+ cell, even if the clinical
29 features were compatible with PLEVA as well as cases in which the histological features were
30 suggestive for PLEVA but the clinical diagnosis of LyP could not be excluded with certainty.
31 Thus, of 21 cases collected prospectively during 2003-2010, 8 were excluded following the
32 clinicopathological correlation and follow-up studies.
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36 Light microscopic and immunohistochemical studies

37 In all cases 1 to 18 hematoxylin and eosin stained sections were reviewed.
38 Immunohistochemical studies were performed using the following antibodies: CD2 (1:50,
39 Novocastra/Leica-Microsystems, Heerbrugg, Switzerland), CD3 (1:75, Dako, Glostrup,
40 Denmark), CD4 (1:2, Novocastra/Leica-Microsystems, Heerbrugg, Switzerland), CD7 (1:25,
41 Dako, Glostrup, Denmark), CD8 (1:400, Dako, Glostrup, Denmark), CD20 (1:600, Dako,
42 Glostrup, Denmark), CD30 (1:75; Novocastra/Leica-Microsystems, Heerbrugg, Switzerland),
43 CD45RO (1:100; Novocastra/Leica-Microsystems, Heerbrugg, Switzerland), CD45RA
44 (1:100; Novocastra/Leica-Microsystems, Heerbrugg, Switzerland), CD56 (RTU,
45 Novocastra/Leica-Microsystems, Heerbrugg, Switzerland, TIA (1:50, Immunotech Marseille,
46 France), and EBER in situ hybridization (RTU, Novocastra/Leica-Microsystems, Heerbrugg,
47 Switzerland)Appropriate positive controls were included. The number of antibodies used
48 varied among individual cases depending on the available tissue.
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56 Molecular biologic studies

57 To ensure uniform results, all cases were studied for TCR clonality and for PVB19 in a single
58 laboratory (Dermatopathology, Friedrichshafen, Germany). The detailed description of the
59 technique was described elsewhere. (44), (65) In brief, the TCR clonality studies were
60 performed by using three multiplex PCRs with different primers from the variable region in
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1 each reaction (reaction 1; Vg1–8, reaction 2; Vg9, and reaction 3: Vg10, Vg11, and Vg12)
2 and the same Cy-5-labeled primers from the conserved region (JGP1/2, JG1/2, and JGP). This
3 approach reliably permits elimination of pseudoclonality. A PCR analysis with the primers
4 specific for VP1/VP2 regions of PVB19 genome was used to study the presence of the virus
5 DNA in the lesional tissue. (65)
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7 8 Control group

9 The 20 patients with LyP (10 women and 10 men, age range 12-64 years, mean 40.5) with
10 available tissue blocks were randomly selected from our files. In all cases, clinicopathological
11 correlation ensured the correct diagnosis. The cases were studied for TCR gene
12 rearrangements and PVB19 as described above.
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15 16 **Results**

17 Clinical data

18 There were 10 female and 3 male PLEVA patients whose age at diagnosis ranged from 7 to
19 89 years (mean 41 years; median 39 years). The clinical manifestation at the time of biopsy is
20 indicated for each case in Table 1. In many cases, the features were of those PLEVA, with
21 small erythematous macules quickly evolving into necrotic papules (Figures 1, 2). Although
22 the clinical diagnostic consideration in some cases included LyP, there was no waxing and
23 waning course on follow-up in any of the cases.
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28 Histopathologic and immunohistochemical findings

29 In all cases, there were features of interface dermatitis with vacuolar alteration at the
30 dermoepidermal junction accompanied by a lichenoid infiltrate, keratinocyte necrosis and
31 erythrocyte extravasation. In addition to the lichenoid infiltrate at the junction, in many cases
32 there were perivascular lymphocytes in the deep vascular plexus resulting in an overall
33 wedge-like appearance of the infiltrate. The lymphocytes were small and well-differentiated
34 but in 9 cases few medium sized monomorphic lymphoid cells were also recognized. Only
35 occasional mild pleomorphic lymphocytes were noted, whereas neither large nor strikingly
36 pleomorphic cells were present. Periadnexal distribution of cells has also been noted in some
37 cases. Remarkably, in 8 cases signs of small vessel lymphocytic vasculitis with vascular wall
38 destruction and fibrin deposits were recognized. This was a focal and discrete finding often
39 seen only in step sections. Variably present features included mild acanthosis, focal
40 epidermotropism of lymphocytes or neutrophils, spongiosis, and parakeratosis, and prominent
41 edema in the papillary dermis (Figures 3A, 4A,B).
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49 Immunohistochemically, in 7 cases more than half (60-80%) of small and medium sized
50 lymphocytes expressed CD30 (Figures 3B, 4C). In 4 cases, CD30 labeled around 40% of the
51 cells and in the remaining 2 cases, there were only 15-20% of CD30 positive cells which
52 nevertheless formed small but distinct clusters. Both intradermal and intraepidermal
53 lymphocytes stained for CD30 but in rare biopsy specimens (even from the same patient)
54 there was predominant staining of either component (Figure 5) Eight of the 13 PLEVA cases
55 displayed a high number of CD8-positive cells and showed co-expression of CD8 and CD30
56 in the intraepidermal and dermal component of the infiltrate (Figures 3C, 4D). The results of
57 staining for the remaining markers are present in Table 1.
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Molecular biological findings

Of the 11 cases of PLEVA studied for TCR gene rearrangement, 6 evidenced a monoclonal T-cell population and 5 were polyclonal. PVB19 was identified in 4 of the 10 cases investigated.

In the control LyP group, 7 of the 20 cases manifested monoclonal TCR rearrangements, 10 proved to be polyclonal, and in the remaining 3 cases the quality of the extracted genomic DNA permitted no reliable interpretation. No PVB19 was identified in 17 specimens, whereas inconclusive findings were seen with the remaining 3 specimens, also possibly to suboptimal DNA quality.

Discussion

Histopathologically, all included cases of PLEVA manifested typical features of the disease. An unusual aspect was the presence of CD30 positive cells which required the distinction from LyP. Traditionally, 3 histopathologic subtypes of LyP are recognized, including type A (histiocytic), type B (mycosis fungoides like), and type C (anaplastic large cell lymphoma—like). (21) Recently, a fourth variant, the so-called LyP, type D has been proposed. (59) Saggini et al (59) reported 9 patients (mean age 29 years) who presented with typical clinical features of LyP (waxing and waning, self-resolving papules) but there were unusual histopathological findings, with prominent epidermotropism occasioning a resemblance to pagetoid reticulosis or primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma. (3)

Our cases further demonstrate a great overlap of PLEVA with some LyP forms but in none of the included cases were there typical clinical features of LyP with waxing and waning course evident on follow-up. Additionally, no large CD30 cells were present. However, if our exclusion criteria are also taken into account, the sharp histopathological demarcation of some cases of PLEVA and LyP appear very difficult and the diagnosis might require clinicopathological correlation or even follow-up. Despite common claims that the two diseases are easily distinguished one from another histopathologically, it becomes evident that with the recognition of new variants the relation between PLEVA and LyP might be closer as traditionally thought. (6), (4), (5), (13), (22) , (69), (70), (78), (79) Although LyP is considered a lymphoma at present, it has an overall survival rate of 100%, and basically the most important argument for classification of the disease as malignant is its rare association with overt and in some cases clonally related cutaneous or extracutaneous lymphomas. (27), (72), (80) Parenthetically, association or progression to mycosis fungoides or another lymphoma type has been documented in PLEVA. (14), (26), (33), (40), (45), (54), (60), (64), (66), (8)

Remarkably, eight of our 13 PLEVA cases (62%) displayed a high number of CD8-positive cells and showed coexpression of CD8 and CD30 in the intraepidermal and dermal component of the infiltrate. Therefore and due to the presence of necrotic keratinocytes, some of our cases histologically simulated primary cutaneous aggressive epidermotropic CD8-positive T-cell lymphoma (CD8+ AECTCL). The simultaneous expression of CD30 in our PLEVA cases, however, differed from CD8+ AECTCL, which is consistently negative ((3)

Emilio Berti, MD, Milan, Italy, personal communication). Finally, the clinical presentation clearly argued against CD8+ AECTCL. Apart from LyP, from a histopathological prospective, another differential diagnosis for the CD30+ PLEVA cases is the small cell variant of CD30+ large cell lymphoma which occurs in the skin extremely rarely and differs from the above PLEVA variant by the clinical manifestation with solitary nodules or tumors. (2), (38), (43).

An interesting observation in our cohort of PLEVA with numerous CD30-positive cells is the frequent occurrence of small vessel vasculitis with fibrinoid necrosis of vessel walls and lymphocytic infiltration, although these findings were discrete. This appears to be in line with the observation of some authors who detected slight vascular deposits of IgM and C3 in most lesions they studied. (16), (49) True lymphocytic vasculitis can occasionally be seen in PLEVA. Leukocytoclastic vasculitis is rare but appears to be overrepresented in cases of the febrile ulceronecrotic variant. In contrast, vasculitis is a rare finding in LyP.

Immune complex mediated vasculitis theory is one of the major theories of the etiology and pathogenesis of PLEVA. (16), (15), (24), (32), (51) The other 2 main hypotheses are (i) the theory of an inflammatory reaction triggered by infectious agents and (ii) **PLEVA representing a lymphoproliferative disorder which has therefore been designated as T-cell dyscrasia by some authors.** (11), (37) As far as the infectious theory is concerned, immunologic or hypersensitivity reaction against an infectious agent in particular, perturbation of the immunological homeostasis of keratinocytes with the subsequent activation of TCR-restricted effector cytotoxic T cells has been suggested as a pathogenetic mechanism. However, the causative agent of the disease remains unknown (for review see (11). Tomasini et al. studied PVB19 in PLEVA and detected the virus in 3 of 10 investigated cases. (65) We identified PVB19 in 4 of the 10 cases tested, and, interestingly, there were 2 patients with known positive serology for the virus. In our control LyP group, in none of the specimens was PVB19 found.

PVB19 is a member of the parvoviridae family, being the causative agent of early childhood fifth disease and papular-purpuric gloves and socks syndrome. (31), (50), (61) An association of PVB19 infection with connective tissue disease-like symptoms has recently been demonstrated. (47) Noteworthy, the authors of that paper showed a consistent constellation of histopathological features including vacuolar interface alteration, a lymphoid lichenoid and a perivascular infiltrate regardless of the clinical presentation of a particular case. (47) Other viruses have been episodically detected in the PLEVA but no firm association has so far been identified. (9), (10) The presence of PVB19 DNA in conjunction with a positive serology in two patients may suggest that PVB19 is pathogenetically linked to PLEVA at least in a subset of cases. The presence of CD30-positive lymphocytes and CD8-positive lymphocytes would be consistent with an inflammatory antiviral response, since CD30-positive, even atypically appearing lymphoid cells have been identified in viral skin diseases such as molluscum contagiosum and herpes virus infections. (39), (76).

Occurrence of clonal T-cells in PLEVA is the main argument to support the theory that the disease represents a lymphoproliferative process. However, the data on the presence of monoclonal T-cell populations in PLEVA are conflicting, with a wide variation between the

1 studies. (19), (42), (46), (62), (73), (74) Tomasini et al. suggested that this can be explained
2 by variations in methodology and histopathological criteria used by different authors. (65) As
3 far as the former aspect is concerned, so called T-cell pseudoclonality can apparently not be
4 excluded in the previous reports. When this bias is eliminated technically, the monoclonality
5 detection rate in PLEVA has been found to be about 10%. (65) . Using the same technique,
6 we detected monoclonal T-cell population in 6 of the 11 cases (55%) studied, the detection
7 rate being higher than in the control LyP group in which 7 of the 17 investigated cases (41%)
8 proved monoclonal. This is in accordance with earlier studies which demonstrated that clonal T
9 cells can only be detected in a minority of LyP cases and appear to be restricted mostly to LyP
10 type C. (30) In the most common LyP, type A, the investigators found no clonal T cells
11 among 9 cases studied. (30) Of the 5 cases of LyP type D studied for TCR gene
12 rearrangements, 2 were monoclonal and 3 polyclonal. (59) Altogether, these findings indicate
13 that the results of clonality studies cannot be a differential diagnostic criterion.
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19 In conclusion, we have described what we believe to represent an unusual variant of PLEVA
20 characterized by the typical clinical features/course but an unusual conspicuous CD30+
21 infiltrate of small to medium sized lymphocytes. Additionally, about half of the cases
22 demonstrated a T-cell clonal population and presence of PVB19 DNA. Although the virus
23 was typically absent in the control group of LyP, the detection rate does not allow to draw a
24 conclusion that PVB19 is a causative agent for PLEVA. The main differential diagnosis
25 condition of this unusual PLEVA variant is LyP, and from a histological point of view also
26 the papular form of mycosis fungoides as well as primary cutaneous aggressive
27 epidermotropic T-cell lymphoma. Admittedly, the CD30+ PLEVA described herein and LyP
28 show a great overlap if one takes into account all known variations. This suggests that LyP
29 and PLEVA may be much more biologically closely related entities than currently thought or
30 even can occur on a clinicopathological spectrum.
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41 additional clinical informations on the patients described in this series: Dr. Martin Grob, MD;
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43 Meier, MD; and Dr. Andreas P. Müller, MD.
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Figure legends

1 Figure 1. Multiple small macules that rapidly evolve into crusted papules (Case 8)

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3 Figure 2. Close-up of necrotic papules with crusts and peripheral collaret (Case 1)

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5
6 Figure 3. Typical features of pityriasis lichenoides et varioliformis acuta, including
7 parakeratosis, acanthosis, vacuolar alteration at the dermoepidermal junction, spongiosis,
8 occasional necrotic keratinocytes and epidermotropism of small lymphocytes can be
9 recognized (A). Staining for CD30 (B) and CD8 (C). (Case 2)

10
11
12 Figure 4. In this case more severe vacuolar alteration, keratinocyte necrosis and erythrocyte
13 extravasation are evident. Note also occasional medium sized lymphocytes within the
14 epidermis (A, B). Staining for CD30 (C) and CD8 (D) (Case 8)

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17 Figure 5. Predominant staining for CD30 of the intraepidermal component. This is the same
18 patient (Case 2) as depicted in Figure 3.

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21 Figure 6. Monoclonal TCR rearrangement (Case 2) evident as a peak in the upper line. The
22 middle line represent a reference line and the lower line is a negative control.

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Table 1. Main clinicopathological, immunohistochemical and molecular biological data

Case	Age/Sex	Clinical features/impression	Infiltrate	Lymphocytes	Other dermal changes	Epidermal changes	ICH	TCR	PV B19
Case 1	M/65	Crusted papules, purpura. Necrotic vasculitis?	Li, Ep, PV, PA	Small, few medium sized	EE, Vas	A, P, VA, NK, Sp, Neu	CD2 90%; CD3 70%; CD4 50%; CD7 40%; CD8 80%; TIA1 50%;CD30 15%;CD20 5%;CD45RO-; CD45RA-; CD56-;CD123-;EBER-	+	-
Case 2	M/44	Generalized partly necrotic papules. PLEVA? LyP?	Li, Ep, PV, PA	Small, few medium sized	EE	A, P, VA, NK, Sp, Neu	CD2 90%;CD3 20%; CD4 20%; CD7 80%; CD8 60%; CD30 40%; CD45RA 5%; CD45RO 90%; CD56-; EBER-	+	-
Case 3	F/31	Multiple lesions on the upper limbs. Lymphoma?	Li, PV	Small, few medium sized	EE, PDE	A, P, VA, NK Subepiderm edema	CD4 20%; CD8 90%; CD30 80%	+	+
Case 4	F/39	Generalized eruption. PLEVA? LyP? Varicella?	Li, PV, PA syring	Small, few medium sized	EE, Vas	VA, NK	CD4 70%; CD8 90%; TIA1 70%; CD30 70%	+	+(serology +)
Case 5	F/51	Three month history of partly necrotic pruritic papules and macules.	Lz, PV	Small	EE	P, VA, NK	CD2 90%; CD4 90%; CD7 30%; CD8 60%; TIA1 50%;CD30 80%; CD45RO 50%-; CD45RA10; CD56-; EBER-	-	-
Case 6	F/13	Generalized papular macular eruption. PLEVA? LyP? PG? Lues?	Li, PV, PA	Small	EE	A, P, VA, Sp, Nk, Neu	CD2 70%; CD3 20%; CD7 70%; CD8 60%; TIA1 60%;CD30 40%; CD45RO 30%; CD45RA 20%; CD56-;; EBER-	+	+
Case 7	M/60	Two month history of symmetric varioliform papules.	Li, Ep, PV, PA	Small, few medium sized	EE, PDE, Vas	P, VA, Sp, Nk,	CD2 60%; CD3 70 %; CD4 80%; CD8 70 %; TIA1 5%;CD30 60%;CD20 5%; ;EBER-	-	+
Case 8	F/28	PLEVA?	Li, Ep, PV, PA	Small, medium sized	EE, PDE, Vas	A, P, VA, NK, Sp, Neu	CD2 30 %; CD3 30%; CD4 30%; CD7 40%; CD8 80%; TIA1 10%;CD30 80%;CD20 5%; CD56 -;; EBER-	-	-(serology +)
Case 9	F/7	Three month history of generalized popular lesions	Li, Ep, PV,	Small	EE, Vas	A, P, VA, NK, Sp,	CD3 %; CD4 20%; CD7 30%; CD8 50%; CD30 40%; EBER-	ND	ND
Case 10	F/14	Multiple papules	Li, Ep, PV,	Small	EE, Vas	A, P, VA, NK, Sp, Neu	CD8 70%; TIA1 40%;CD30 40%;	ND	ND
Case 11	F/89	Generalized hemorrhagic papular lesions. Vasculitis?	Li, Ep, PV	Small, few medium sized	EE, PDE, Vas	P, NK, VA, Sp, Neu	CD4 50%; CD8 90%; CD30 60%;; TIA 60%	-	-
Case 12	F/38	Prurigo simplex acuta?	Li, PV, PA, Ep	Small, few medium sized	EE, Vas	A, P, NK, VA, Sp Neu	CD2 90%; CD3 90%; CD4 40%; CD8 60%; CD30 70 %; CD45RA 10%; CD45RO 100%;; TIA 80%;	+	-
Case 13	F/59	9 month history of hyperkeratotic papules and macules on the limbs and trunk. PLEVA?	Li, PV, Ep	Small, few medium sized	EE	A, P, NK, VA, SP, Neu	CD2 90%; CD4 90%; CD7 60%; CD8 60%; CD30 20 %; TIA 10%;	-	ND

PLEVA pityriasis lichenoides et varioliformis acuta

LyP lymphomatoid papulosis

PG psoriasis guttate

Li lichenoid

PV perivascular

PA periadnexal

Ep focal epidermotropism
EE erythrocyte extravasation
Vas vasculitis
PDE papillary dermis edema
A acanthosis
P parakeratosis
VA vacuolar alteration
NK necrotic keratinocytes
Sp spongiosis
Neu Neutrophils
TCR T- cell receptor rearrangement studies
PVB 19 Parvovirus B19

Figure 1

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Figure 2

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Figure 3
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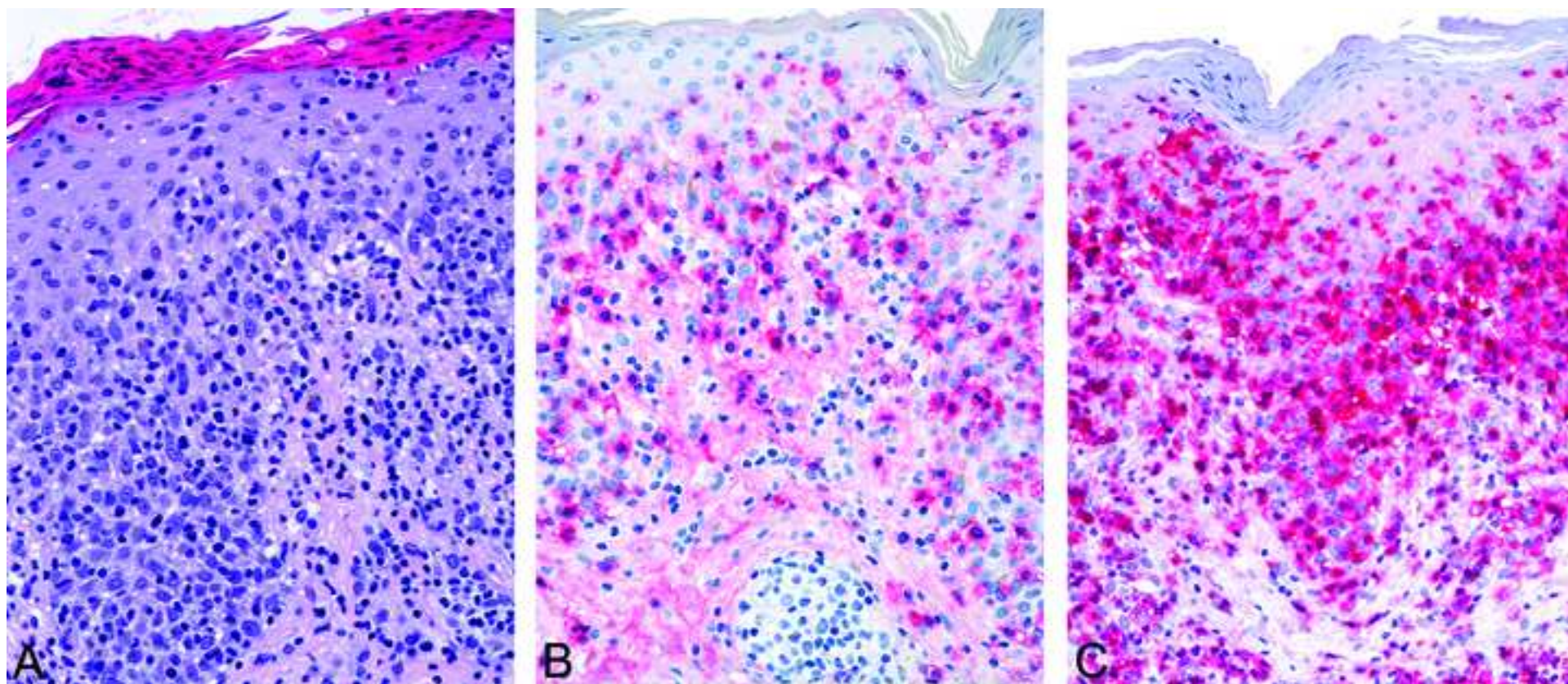


Figure 4
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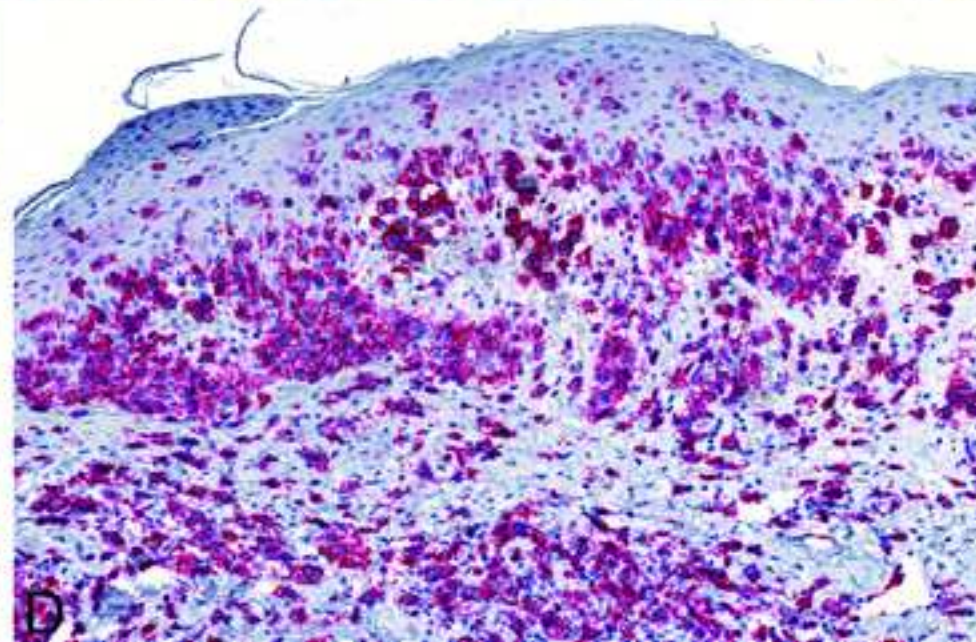
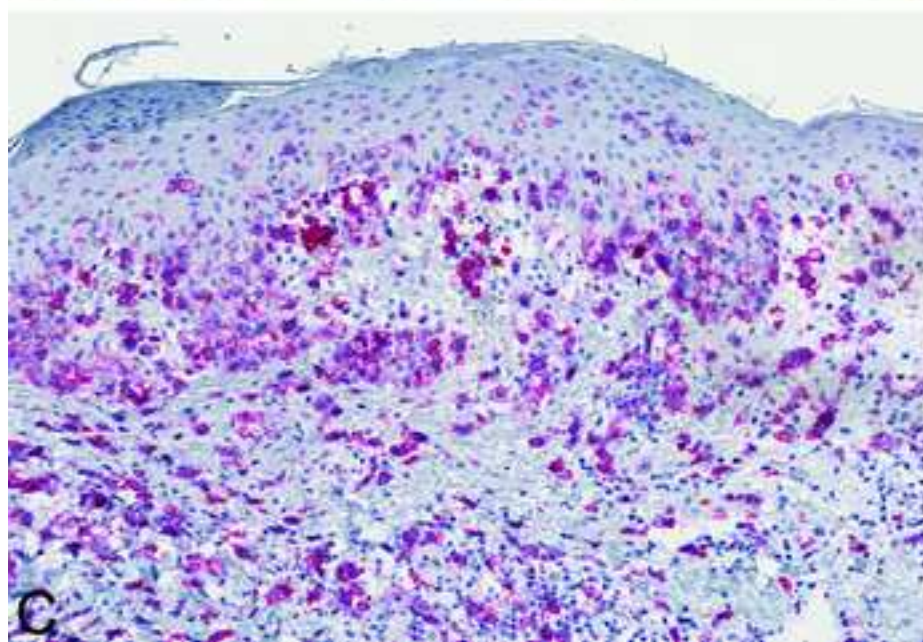
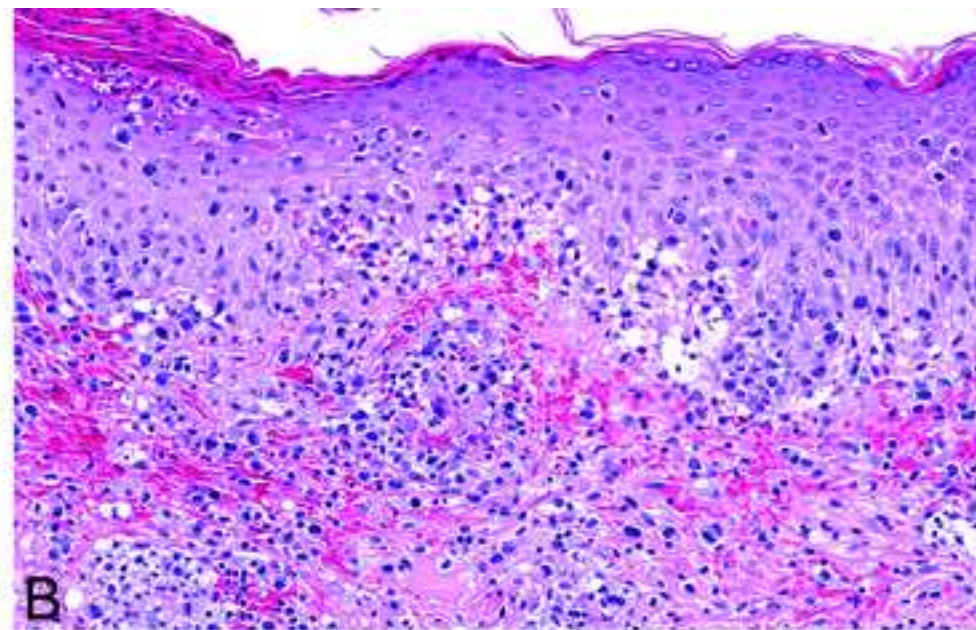
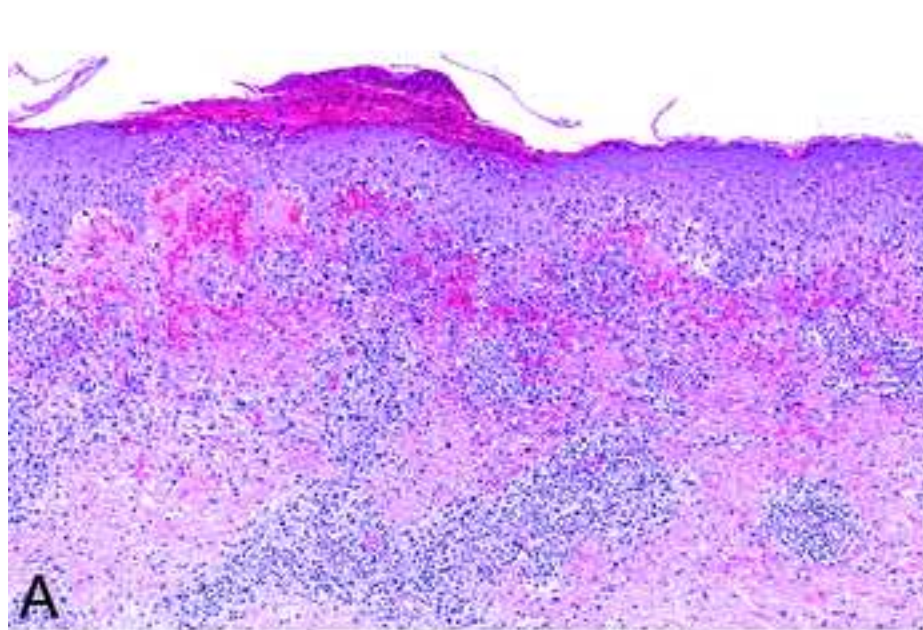


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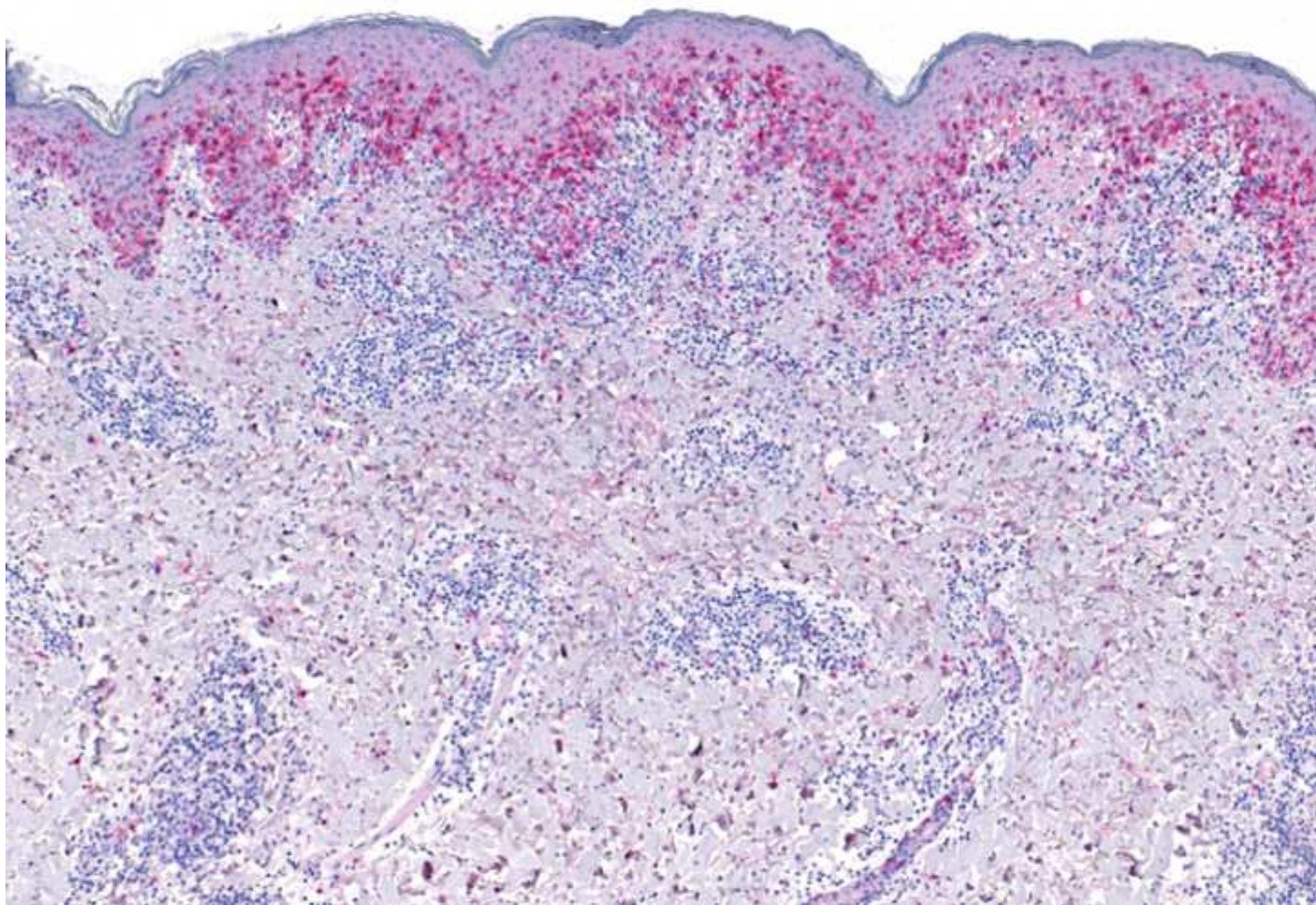
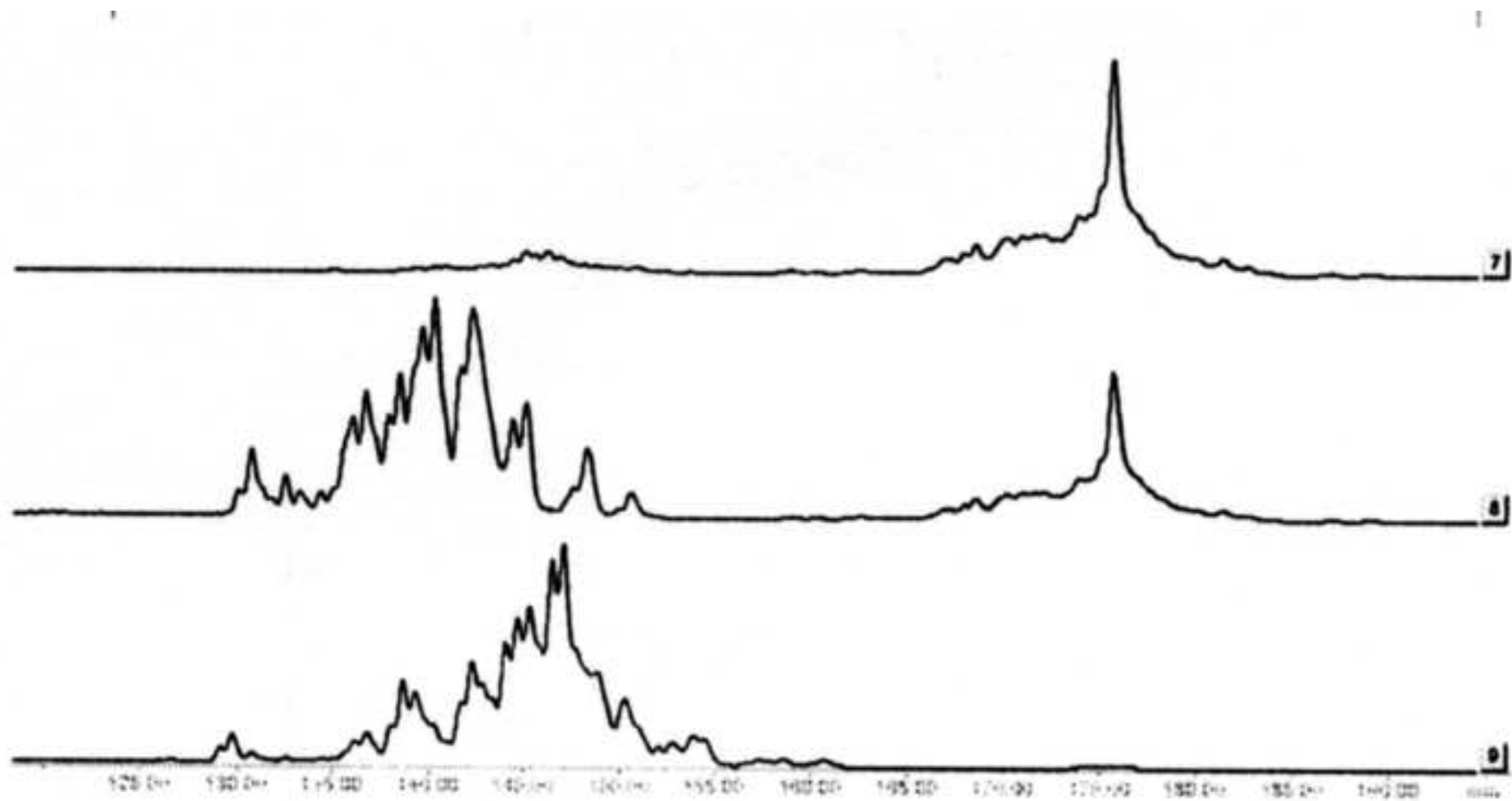


Figure 6
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