Angioinvasive Lymphomatoid Papulosis: A new variant simulating aggressive lymphomas

Kempf, Werner ; Kazakov, Dmitry V ; Schärer, Leo ; Rütten, Arno ; Mentzel, Thomas ; Paredes, Bruno E ; Palmedo, Gabriele ; Panizzon, Renato G ; Kutzner, Heinz

Abstract: Lymphomatoid papulosis (LyP) belongs to the spectrum of primary cutaneous CD30-positive lymphoproliferative disorders. Clinically, LyP is characterized by a variable number of self-healing papulonodular lesions, with the typical waxing and waning course. Histologically, 4 types (A, B, C, and D) have been delineated. Angioinvasive growth and large ulcers are rare findings in LyP and simulate aggressive lymphoma. We retrospectively analyzed the clinicopathologic and molecular features of angioinvasive LyP in a series of 16 patients. This new form of LyP is characterized by oligolesional papules that rapidly ulcerate and evolve into large necrotic eschar-like lesions with a diameter of 1 to 4 cm and an angiocentric and angiodestructive infiltrate of small-sized to medium-sized atypical lymphocytes expressing CD30 and frequently CD8. As in other forms of LyP, the lesions underwent spontaneous regression after a few weeks. Recurrences were common, but the prognosis was excellent with no extracutaneous spread or disease-related deaths. Complete remission occurred in 9 of 16 patients (56%). This LyP variant should be distinguished from aggressive forms of angiocentric and angiodestructive and cytotoxic T-cell lymphomas. We propose the term LyP type E for this clinically and histologically unusual variant.

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Cover Letter R1

Manuscript revision. AJSP-D-12-00462 R1, entitled " Angioinvasive lymphomatoid papulosis - a new variant simulating aggressive lymphomas"

June 9th, 2012

Dear Dr Mills,

Enclosed please find the revised version of our manuscript.
We are very grateful for your comments and the comments of the reviewers. Enclosed please find the point-by-point answers to their comments. The corresponding changes in the manuscript has been highlighted in red.

We hope that the revised manuscripts fulfills the requirements and very high standard for publication in the Journal. We very much appreciate your evaluation of our manuscript.

Sincerely yours,

Werner Kempf, MD

Point-by-point answers to the reviewer's comments

Reviewer #1:
This is a nicely written and beautifully illustrated series of cases with similar clinical presentation with self-healing eschars (on minimal treatment) and pathologic features of angionecrosis comprising CD30+ CD4/CD8+ cells. However, I feel it is premature to add yet another alphabet letter (E) to the LyP lexicon which already contains C. This approach would might lead to calling neutrophil-rich LyP, LyP type N. Instead I recommend maintaining the descriptive term of angioinvasive LyP.

We thank the reviewer for his/her time and high estimation of our work. In regard to the critics of the proposed term LyP type E – the referee is right in indicating that this might be premature to add a new type in addition to a provisional type D. However, we do not include this proposal in the title and discuss it only briefly, rather putting emphasis on mnemonics (E – for the typical clinical presentation with eschar-like lesions). Obviously, both the second referee and Editor-in-Chief accepted this way and we would like ask all the referees to let us to suggest and discuss this term as is. Thank you.

Several additions/corrections are recommended.
1. Despite the lack of systemic involvement noted thus far, ALK staining should be done- as some primary cutaneous ALCL are ALK+.

As suggested by the reviewer we have added CD246 (ALK-1) staining in all cases and included this information in Table 3, in the Results and Material and Methods. None of the cases expressed ALK-1.

2. Table 3, 2nd to last column should read TCR gamma/delta.

Corrected as indicated by the reviewer

3. Final paragraph- popular should be papular.

Corrected as indicated by the reviewer

We thank you once again for your time and helpful suggestions

Reviewer #2:
Kempf et al. have studied a group of patients with an unusual variant of lymphomatoid papulosis (LyP) with an angioinvasive growth pattern simulating aggressive lymphomas with overlapping histologic features. I have the following comments/suggestions:

Major comments:

1. The authors should explain in more detail why the larger, solitary or limited ulcerated lesions are not primary cutaneous ALCL (C-ALCL) rather than LyP. As the authors briefly mention in the Discussion (page 12, paragraph 2), tumor cells in C-ALCL often surround and to a certain extent may invade blood vessels, patients with C-ALCL may have LyP at some time in the course of their disease, approximately 20% of C-ALCL spontaneously regress, and a small number of C-ALCL may be CD8+. In addition, it is difficult to tell from the Figures and from the morphologic description, how many CD30+ large cells are present and if they are beginning to form large clusters or sheets (features that are important to distinguish C-ALCL and LyP). Also, the rarity of eschar formation in C-ALCL should be mentioned as a feature possibly useful in the differential diagnosis. Why were the 5 patients with solitary lesions (page 4, lines 21 to 23) excluded, as they would represent approximately 20% of the patients seen over the last 12 years? Was there concern they were C-ALCL? Were the CD30+ large cells too numerous and sheet-like?

The reviewer is right in indicating all these feature. In fact these features fit with the accepted concept that LyP and cutaneous ALCL represent a spectrum. However, the course of the disease in our patients with several spontaneously regressing lesions indicates that the condition is much closer to LyP within this spectrum. Additionally, it would be highly unusual to expect spontaneous regression in so many lesions of so many patients had they have ALCL. The 5 patients were excluded because they have a solitary lesion during the entire course which argues against LyP defined in the current lymphoma classifications to which we would like strictly to adhere in our diagnostic criteria. Thus, these patients were excluded. Sheets of cells were not a criterion to exclude, because this feature is seen in authentic LyP, namely type C.

2. In the Results section of the text, page 8, Molecular biological findings, it is stated that monoclonal TCR gamma gene rearrangements were found in 9 of 15 cases (60%) studied. Table 3 has negative ("-") for all the cases studied. Please explain the discrepancy. As the Discussion mentions clonality in LyP, I assume the Table is in error.

We apologize for the confusion. In table 3 TCR means immunohistochemical staining for TCR gamma/delta – this has been corrected after suggestion of the first referee.

3. In the Discussion, page 10, paragraph 2, invasion of smooth muscle bundles and perivascular spaces is described but not presented in the Results.

We did it on purpose to be succinct and avoid redundancy – we did not intend to mention in the text of the Results all the features, and therefore refer to Table 2 which lists the alterations mentioned by the referee.

Minor comments:

1. A subset of atypical cells can be CD30+ in extranodal NK/T-cell lymphoma nasal type and in other T-cell or NK-cell tumors. A statement saying it is rare for the majority of atypical cells in other tumors to be CD30+, a finding which is usually limited to CD30+ lymphoproliferative disorders, should be added to the Discussion, pages 11-12 where the differential diagnosis of "LyP type E" is reviewed.

As suggested by the referee the following sentence has been added:
A subset of atypical cells express CD30 in extranodal NK/T-cell lymphoma nasal type and in other T-cell or NK-cell tumors but it is rarely expressed by the majority of atypical cells in these neoplasms.

2. Reference the case reports alluded to in the first paragraph of the Discussion, line 55, as being the initial descriptions of this form of LyP.

We have shortened the original sentence: Our series of 16 patients describes the clinicopathologic findings of a rare and unusual LyP variant, which has so far only been documented in very few case reports into Our series of 16 patients describes the clinicopathologic findings of a rare and unusual LyP variant because strictly speaking only angiocentricity had previously been documented but the typical clinical presentation as we report here were not. Therefore, to avoid confusion we deleted part of the sentence.

3. Please shorten Table 1. Delete the word "case" in column 1 for each patient and just use the number, as the column header is "Case". In particular in the "Clinical features and course" column condense the relapse information. For example, Case 1 Oral cavity ulcer, multiple relapses with one or two lesions, oral cavity and skin (feet, hip, scrotum, perineum, nose). The size of the primary lesion would be important to give, when known. Case 6 delete "for the hand lesion" after surgical excision. In the legend delete one "t" on ultraviolet.

As suggested by the reviewer, the word case has been deleted and "for the hand lesion" after surgical excision has also been deleted. As the patients have several lesions it is impossible to give size for each lesion in Table- but the range is described in the Results and Discussion.

4. In the text on page 6 in the second paragraph of the Results, lines 33-34, tell which three patients had multiple small papules.

The sentence actually said originally: In addition to large ulcerative lesions, three patients, at one point of the disease, manifested few (up to 10) smaller papules similar to those seen in classic LyP.
As suggested by the reviewer we have now specified the particular cases and replaced few by several to avoid confusion.

5. The paper is quite long and somewhat redundant. Although the clinical images are beautiful, I would recommend deleting three figures and would suggest that Figures 2, 5, and 6a and 6f remain. Corresponding references in the text to figures that are removed would also need to be deleted. I would also recommend deleting Figure 10.

As suggested by the reviewer we have deleted the original composite Figure 1 and composite Figure 4, composed of 5 and 3 parts respectively. We would like to keep the remaining clinical figures, as they are essential for this particular condition. Overall, of the 18 individual parts comprising the original clinical images now there are only 11 (about 40% reduction). We would like to keep original Figures 3 and 5 (Figures 1 and 3 in the revised version) as they consist only of one part each and show essential features - the typical eschar like appearance (Figure 1)1and multiple papules (Figure 3), the latter providing the link with LyP. We would like to keep Figure4 (original 6) as is as it nicely demonstrate the evolution of the lesions, showing that this is not a course of a lymphoma but rather LyP. We believe further reduction of the clinical figures would not give sufficient emphasis to the unique clinical presentation as an essential part of this LyP form. As suggested by the referee we have deleted Figure 10.

6. In Figure 7E, there appear to be large numbers of CD30+ cells. The image is somewhat difficult to see individual cells. Were all the CD30+ cells large? How did the authors distinguish this from C-ALCL or LyP type C? A higher magnification insert would be useful here.

The cytological details of this case are seen in part D of this figure. Parts E and F are included to demonstrate the content of CD30 and CD8 cells. The reviewer is right in indicating the histological and phenotypic overlap with ALCL and type C due to large collections of CD30+ cells, the difference to ALCL and LyP

type C are the oligolesional presentation with large ulcerating lesions and the marked angiocentricity in our cases.

7. A higher magnification image of TIA-1 should be provided as an inset in Figure 8 to illustrate the characteristic punctate, cytoplasmic pattern of staining.

We will be happy to provide an additional image if the referee and Editor in Chief advice us again to do so. The reason for not doing it now is the following: adding an inset as suggested by the referee would close important detail (angiocentricity of TIA + cells) , so one in fact would require an additional image but as far as we understand we were asked to reduce the number of the illustrations.

8. Overall, the images do not seem to be of high resolution. The alkaline phosphatase chromagen is staining so intensely, it is difficult to see morphologic detail.

The images appear blurred only in the downloaded pdf.file of the manuscript. The quality of the submitted figures is excellent if the submitted tiff.files are accessed by clicking on the link on the left upper side of the pages containing figures. We also downloaded high resolution images from the website to ensure that all the figures have an adequate size and high resolution (300 dpi).

Editorial/typographical changes:

Page 3, lines 37 to 39, Despite the presence of medium-sized to large pleomorphic or anaplastic cells suggesting a highly malignant course, LyP exhibits. . .

Corrected as suggested by the reviewer.

Page 3, line 61, or died of lymphoma (delete "the")

Corrected as suggested by the reviewer.

Page 4, line 37, patients' charts

Corrected as suggested by the reviewer.

Page 5, line 32, interstitial

Corrected as suggested by the reviewer.

Page 6, paragraph 3 of the Results, line 50, please define "s.c. "

Corrected as subcutaneous.

Page 8, paragraph 1, line 17, delete (Figure)

Corrected as suggested by the reviewer.

Page 11, line 42, The differential diagnosis of LyP type E includes (add "s")

Corrected as suggested by the reviewer.

Page 11, line 44, what is meant by adult T-cell lymphoma? Do the authors mean adult T-cell leukemia/lymphoma?

Yes. Thank you. Corrected as suggested by the reviewer.

Page 11, line 50, extranodal NK/T-cell lymphoma nasal type can express CD8, therefore, please change to CD8+/-

Corrected as suggested by the reviewer

Page 11, line 50, necrosis

Corrected as suggested by the reviewer.

Page 12, lines 17-19, adult T-cell leukemia/lymphoma

Corrected as suggested by the reviewer

Page 13, line 13, papular lesions

Corrected as suggested by the reviewer

Page 13, line 43, highly (add "ly") malignant angiocentric

Corrected as suggested by the reviewer

References: Not all or the references have complete citations, for example 14, 61, 68; British Journal of Dermatology is abbreviated Br J Dermatol (references 6, 64). Reference 11 is from 2011 not 2012. PLEASE CHECK ALL

REFERENCES FOR ACCURACY IN CITATION.

We used the EndNote program for references, the latest version with the specific style for AJSP. Abbreviations of the journals should appear to be ok. The incomplete citations are papers in press which we had to add manually – if our manuscript will be accepted we will check once again all updates while proof reading. Thank you.

Table 2, Syringotropism 8/(38%) (add the "/")

Corrected as suggested by the reviewer

Table 2, Skeletal muscle atypical lymphocyte infiltration (correct spelling)

Corrected as suggested by the reviewer

Table 3 Remove "case" before the number in Column (see minor comments) and expand the column width for beta-F1

Corrected as suggested by the reviewer

Table 3, legend, Do the authors mean = signifies cases with approximately equal number of interstitial CD4 (rather than CD8) and CD8 cells?

Yes. Thank you. Corrected as suggested by the reviewer

Figure 7 legend, line 43, erythrocyte (delete "s") extravasation

Corrected as suggested by the reviewer

Figure 8 legend, line 52, correct to "vessels" (A, B) and substitute adipocytes for "lipocytes"

Corrected as suggested by the reviewer
We thank the reviewer for his/her time, careful reading, and helpful suggestions.

Editor's comments:

I agree with the reviewers about the need to reduce and improve the illustrations. In particular, the large number of clinical photos is excessive for a pathology journal.
Thank you. –SEM

As suggested by one of the reviewers and the editor we have deleted 2 original clinical composite figures together consisting of 11 parts and this resulted in a 40% reduction of the clinical images. We would like to keep the remaining clinical figures, as they are essential and kindly asking the Editor for permission to keep the remaining clinical images. We have also deleted one histological image that might have been indeed of suboptimal quality following the suggestion of reviewer 2. We thank you for your time with evaluation of our manuscript.

Angioinvasive lymphomatoid papulosis – a new variant simulating aggressive lymphomas

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Short title: Angioinvasive lymphomatoid papulosis

Key words: lymphoma, skin, CD8, CD30, lymphomatoid papulosis, cytotoxic lymphoma

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Abstract

Lymphomatoid papulosis (LyP) belongs to the spectrum of primary cutaneous CD30-positive lymphoproliferative disorders (CD30+ LPD). Clinically, LyP is characterized by a variable number of self-healing papulo-nodular lesions, with the typical waxing and waning course. Histologically, four types (A, B, C, D) have been delineated. Angioinvasive growth and large ulcers are rare findings in LyP and simulate aggressive lymphoma. We retrospectively analyzed the clinicopathologic and molecular features of angioinvasive LyP in a series of 16 patients. This new form of LyP is characterized by oligolesional papules that rapidly ulcerate and evolve into large necrotic eschar-like lesions with a diameter of 1-4 cm and an angiocentric and angiodestructive infiltrate of small to medium-sized atypical lymphocytes expressing CD30 and frequently CD8. As in other forms of LyP, the lesions underwent spontaneous regression after a few weeks. Recurrences were common, but the prognosis was excellent with no extracutaneous spread or disease-related deaths. Complete remission occurred in 9 out of 16 patients (56%). This LyP variant should be distinguished from aggressive forms of angiocentric and angiodestructive and cytotoxic T-cell lymphomas. We propose the term LyP type E for this clinically and histologically unusual variant.

Introduction

Lymphomatoid papulosis (LyP) belongs to the spectrum of primary cutaneous CD30-positive lymphoproliferative disorders (CD30+ LPD). (16), (31) Histologically, four LyP types (A, B, C, and D) have been identified. Type A is characterized by the presence of large pleomorphic or anaplastic CD30+ T-cells scattered or in small clusters within the background of eosinophilic and neutrophilic granulocytes, histiocytes and small lymphocytes. Type B shows epidermotropic infiltrates of small to medium-sized lymphoid cells, with variable extent of CD30 expression. In type C, a nodular dense infiltrate of cohesive sheets of pleomorphic or anaplastic CD30+ cells is present and it usually contains only a few eosinophilic or neutrophilic granulocytes. (66), (30), (40), (67), (12) Recently, type D has been described which displays an epidermotropic infiltrate of CD8+ and CD30+ small to medium-sized lymphoid cells. (57) Within the same patient, different lesions may show different histological types, either synchronously or metachronously. (18) The CD30+ lymphoid cells may express a CD4, CD8 or CD56, with CD4 immunoreactivity being the most common phenotype. (11), (38) Independent of its histological pattern and the immunophenotype, LyP is clinically characterized by a variable number of self healing papulo-nodular lesion, with the typical waxing and waning course. The individual lesions undergo spontaneous regression within a few weeks, sometimes accompanied by ulceration on top of the lesions and occasionally leaving behind varioliform scars. Despite the presence of medium-sized to large pleomorphic or anaplastic cells suggesting a highly malignant course, LyP exhibits a favorable prognosis and requires no aggressive treatment. (24), (5)

We report a series of 16 patients with LyP who presented with a clinically and histologically unusual manifestation simulating highly aggressive angiocentric and angiodestructive T-cell lymphoma. These patients developed recurrent papular lesions that rapidly turned into hemorrhagic necrotic ulcers (eschar-like) with a diameter of more than 1 cm and spontaneous regression, often leaving behind a scar. The typical features were rather large size of ulceration exceeding the size of the preexisting papule/nodule and presentation with only a few lesions at a given time. Histologically, predominantly angiocentric and angiodestructive infiltrates of CD30 and mostly CD8-positive lymphoid cells as well as necrotic areas were the hallmark. Remarkably, the skin lesions resolved spontaneously and none of the patients manifested progressive disease with extracutaneous involvement or died of lymphoma, reflecting an indolent

course with an excellent prognosis. In regard to the excellent prognosis it is important to differentiate this form of LyP from other angiocentric primary or secondary cutaneous T-cell lymphoma with an aggressive course and poor outcome.

Patients and methods

Since our first observation in the year 2000, we have identified 16 patients presenting with similar clinical and histological features suggesting an unusual form of LyP. The diagnosis of LyP was based on clinicopathologic correlation with recurrent skin lesions undergoing spontaneous regression, the presence of atypical lymphoid cells with expression of CD30 and a benign course of the disease. Excluded from the study were 5 additional patients with similar histopathological features but clinical presentation with a solitary lesion.

A total of 21 biopsy specimens from the included 16 patients were collected and reviewed, including 18 skin biopsies and 3 specimens from the oral mucosa.

The main clinical data including history (age at first lesion / symptoms, age at diagnosis), morphology of skin lesions and their evolution, occurrence and number of relapses, and last follow-up, as well as results of staging examinations and treatment were retrieved from the referring dermatologists as well as from the patients' charts. In 8 out of the 16 patients clinical images were available for review. Four patients were dermatologically examined by one of the authors (W.K.). Hematoxylin-eosin (H&E)-stained slides and immunohistochemical stainings were analyzed and molecular biologic assays performed. The study was approved by the Ethical committee of the Kanton Zürich, Switzerland (KEK-StV-No. 04/12).

Histology

All biopsies were fixed in 10%-buffered formalin and embedded in paraffin. H&E stained sections with a thickness of 4 micrometer were evaluated and the following findings reported: Ulceration/excoriation of the epidermis (oral mucosa epithelium), epidermal (epithelial) hyperplasia, vacuolar alteration, edema in the papillary dermis, perivascular or diffuse pattern of the infiltrates, infiltration and destruction of vessel walls, intraluminal thrombi, size (small-medium-large) and morphology (pleomorphic, anaplastic) of lymphoid cells, presence of

eosinophils and neutrophils, extension of the infiltrate into the subcutis, peri- or intaneural invasion, and adnexal involvement.

Immunohistochemistry

Immunohistochemical studies were performed on formalin-fixed paraffin-embedded tissue using the following antibodies: CD2 (1:50, Novocastra/Leica-Microsystems, Heerbrugg, Switzerland), CD3 (1:75, Dako, Glostrup, Denmark), CD4 (1:2, Novocastra/Leica-Microsystems, Heerbrugg, Switzerland), CD5 (1:2, 4C7, Dako, Glostrup, Denmark), CD7 (1:25, Dako, Glostrup, Denmark), CD8 (1:400, Dako, Glostrup, Denmark), CD20 (1:600, Dako, Glostrup, Denmark), CD30 (1:75; Novocastra/Leica-Microsystems, Heerbrugg, Switzerland), CD45RA (1:100, X148, Novocastra), CD45RO (prediluted, UCHL1, Leica) CD56 (RTU, Novocastra/Leica-Microsystems, Heerbrugg, Switzerland, TIA (1:50, Immunotech Marseille, France), TCR beta F1 (8A3, 1:50, Thermo Scientific, Fremont, CA, USA), TCR gamma/delta (y3.20, 1:100, Thermo Scientific, Fremont, CA, USA) and CD246 (1:50, ALK-1, Dako, Glostrup, Denmark). Appropriate positive controls were included. The number of antibodies used varied among individual cases depending on the available tissue. For all cases, a general predominance of CD4+ or CD8+ cells in the interstitial infiltrate were documented, as well as particular phenotype of cells in the perivascular and/or angioinvasive lymphocytes within the vessel walls. For the latter, the results were assigned to one of the 4 categories: immunoreaction in all of the affected of the vessels (+); immunoreaction in a majority of the affected of the vessels (+/-); immunoreaction in a minority of the affected of the vessels (-/+); no immunoreaction in any of the affected of the vessels (-).

Molecular biology

The cases were studied for rearrangement of T-cell receptor gamma genes and for the presence of viral DNA of a variety of viruses including Orthopox, Parapox, Parvovirus B19, CMV, VZV, HSV1/HSV2, and EBV in a single laboratory (Dermatopathology, Friedrichshafen, Germany). Additionally, EBER in situ hybridization was performed (RTU, Novocastra/Leica-Microsystems, Heerbrugg, Switzerland). The detailed description of the technique for TCR gene rearrangements was described elsewhere. (35) In brief, the TCR clonality studies were performed by using three multiplex PCRs with different primers from the variable region in each reaction (reaction 1;

Vg1–8, reaction 2; Vg9, and reaction 3: Vg10, Vg11, and Vg12) and the same Cy-5-labeled primers from the conserved region (JGP1/2, JG1/2, and JGP).

Results

Clinical presentation, course of the disease, treatment and follow-up

The main clinical features are summarized in Table 1. There was a male preponderance (ratio men to women 3:1) with 12 male and 4 female patients. The mean age at diagnosis was 51.7 years ranging from 8 to 77 years (median age 61 years). All of them have several clinical features in common which included occurrence of only a very few papulo-nodular lesions that rapidly evolve into larger ulcerations exceeding the size of the antecedent papule (diameter 1-4 cm). The lesions often manifested a hemorrhagic necrotic crust and had an eschar-like appearance, prompting clinical consideration of pyoderma gangrenosum, ulcerative herpes infection or Orf's disease or vasculitis. The ulcers usually persisted for 3-6 weeks before undergoing spontaneous regression, leaving behind a scar. Typically, only few ulcerative lesions (sometimes a single ulcer) were present at a given time, but the patients as a rule experienced several relapses (Figures 1, 2).

In addition to large ulcerative lesions, four patients (Cases 2, 7, 12, 16), at one point of the disease, manifested several (up to 10) smaller papules similar to those seen in classic LyP (Figure 3). Three patients (Cases 1, 10, 15) showed involvement of the lips and/or oral mucosa at primary disease manifestation or during course of the disease (Figure 4). In another two patients (Cases 4 and 13), the primary lesions and the recurrences were limited to one body area corresponding to localized (a.k.a regional) LyP. Due to suspected cutaneous lymphoma, 12 patients underwent staging investigations to exclude extracutaneous involvement with negative results. In five patients no staging examinations were performed.

Only three patients received low-dose methotrexate subcutaneously (15-30 mg per week), whereas all the others were treated with topical antiseptic or topical steroids or UV light therapy including heliotherapy, UVB narrow band, and psoralen UVA (PUVA) treatment. During the follow-up, relapses occurred in all patients within one year. In none of the patients did the disease progress as to involve extracutaneous sites or cause death of the patient. Complete remission

occurred in 9 out of the 16 patients (56%) after a mean follow-up of 37.5 months (median; 24 months; range from 3 to 144 months).

Histopathologic features

The consistent feature in all cases was dermal angiocentric infiltrates of small, medium-sized to large pleomorphic cells that infiltrated the walls of small to medium-sized dermal and subcutaneous blood vessels. The vessels involved included small arterioles and medium-sized veins located mostly in the dermis, but in some cases in which the subcutaneous tissue was present, the affected vessels were seen in the subcutis (Figures 5A, B, 6A, B). Usually, several vessels were involved in a given specimen and many were completely destroyed, which probably accounted for necrosis of the adjacent dermis, overlying epidermis and adnexal structures. Conspicuous thrombosis was a feature in over half of the specimens. In addition to the vessels infiltrated and destroyed by the atypical lymphoid cells, there were vessels in the same specimens, which manifested vasculitis-like changes, including fibrin deposition in the wall but not infiltrated by atypical lymphoid cells. A typical feature was erythrocyte extravasations, which in a majority of cases was extensive (Figure 5 A-D). The number of angioinvasive lymphocytes varied between the biopsies of different patients, but also within the same patient. Only in one small punch biopsy this characteristic feature was absent, but another specimen from the same patient displayed angioinvasive infiltrates.

Apart from atypical lymphocytes, most specimens revealed numerous eosinophilic granulocytes arranged interstitially in the dermis/or subcutis, often forming small collections. Neutrophils were present too, but their estimation was hampered by necrosis and karyorrhexis. Other common features included epidermal (epithelial) necrosis and prominent edema in the papillary dermis.

In some cases there was focal epidermotropism and subtle folliculotropism of small lymphoid cells but in 2 cases there were also medium-sized atypical cells within the epidermis which expressed CD8 and CD30 (*vide infra*) (Figure 7 A-C) . In cases in which the vessels in the subcutis were involved, there invariably was an infiltrate to the adjacent tissue producing a pattern of lobular or mixed panniculitis (Figure 5A). Additionally, focally, there was so-called rimming of the atypical lymphocytes around adipocytes, as is seen in panniculitis-like lymphoma (Figure 8A). Table 2 summarizes the main histopathological features and their frequency.

Immunohistochemical findings

With respect to the *perivascular* and/or *intramural* lymphocytes, the cells constantly expressed CD30 and CD8, whereas expression of TIA-1 was variable (Table 3) (Figures 5 E-G, 6 C,D). However, in cases in which few cells in the angiocentric infiltrates were labeled for CD8, TIA was expressed by a majority of lymphocytes. CD4 was also often expressed by the cells in angiocentric infiltrates, and there was variation with respect to immunoreactivity of CD4 and CD8/TIA-1 even within a single specimen in the sense that some vessels were surrounded and permeated by predominantly CD8 positive elements, whereas in others the reverse was true or there were equal numbers of CD8+ and CD4+ cells.

With respect to the entire infiltrate, that is *both* angiocentric and interstitial, an overall predominance of CD8+ cells over CD4+ cells was seen in 8 out of 16 cases (50%), whereas the reverse was observed in 4 cases and the remaining 4 cases showed approximately equal numbers of CD4+ or CD8+ cells in the interstitial infiltrate.

Irrespective of the location (angiocentric vs interstitial), lymphoid cells were constantly positive for beta-F1 and negative for ALK-1 and TCR gamma/delta, without loss of CD2 or CD5. There was subtle variation with respect to expression of CD3 and CD7 in the angiocentric infiltrate (Table 3). In one case (Case 4), atypical lymphoid cells in the angiocentric infiltrate were CD56 positive.

In cases with epidermotropism or folliculotropism, intraepithelial lymphocytes co-expressed CD30 and CD8 (Figure 7 B, C).

Molecular biological findings

Monoclonal TCR gamma gene rearrangements was found in 9 of the 15 cases (60%) studied. In none of the investigated specimens was any viral DNA or RNA detected.

Discussion

Our series of 16 patients describes the clinicopathologic findings of a rare and unusual LyP variant. Due to the predominantly angiocentric and angiodestructive infiltrates of atypical

lymphoid cells, rapid development of hemorrhagic necrotic ulcers and cytotoxic phenotype, this variant simulates aggressive (mostly cytotoxic) lymphomas and may not be recognized as a lymphoproliferative disorder with an excellent prognosis. In regard to the difference in the histology and clinical presentation to other LyP variants, we propose the designation LyP, type E for this disease variant, in addition to well recognized and established types A, B, C and D. The designation "E" refers not only to the next letter selected to denote this disease variant but also reflects one of the most typical features of the disease, namely *e*schar-like (hence, type E) ulcers. In its classic form, LyP clinically manifests with crops of papules and small nodules, which may occasionally be accompanied by a small and superficial ulceration preceding spontaneous involution of the lesions. In LyP type E, the initial papular lesions rapidly evolve into larger ulcerations often exceeding the size of the antecedent papule, reaching up to 4 centimeters in diameter and manifesting a hemorrhagic necrotic, eschar-like appearance. These ulcers persist for 3-6 weeks before undergoing spontaneous regression. Due to this predominant ulcerative aspect, in many of our patients the clinical differential diagnosis (before the histopathological data were available) included pyoderma gangrenosum, ulcerative herpes infection or Orf's disease as well as vasculitic ulcerations. In many of our patients, only one or two ulcers at the time of diagnosis and during disease course were present, whereas in classic LyP usually multiple small papules are found in different stages of lesion evolution. However, three patients, at one point of the disease, had also few papules such as those seen in classic LyP, thus rather linking this condition to LyP within the spectrum of cutaneous CD30+ LPD.

From a clinical standpoint our cases are very similar if not identical to the patient described recently by Ponte et al as a borderline CD30+ cutaneous lymphoproliferative disorder, namely, a presentation with few lesions rapidly becoming ulcers healing with scars. In addition, cytotoxic phenotype was also a feature in that case. (54) However, in contrast to our patients, angiocentric/angiodestructive features were not reported in the histologic specimens by the authors. (54)

Histopathologically, LyP type A and C are the most common histopathologic variants with wedge-shaped or nodular infiltrates of large pleomorphic or anaplastic CD30+ lymphoid cells arranged as scattered atypical cells in the background of eosinophils and neutrophils (type A) or in cohesive sheets (type C). The rather uncommon LyP types B and D show an epidermotropic

infiltrate of atypical lymphocytes with variable expression of CD30, and both histologically resemble mycosis fungoides. In contrast to these four histologic types, LyP type E displays a predominantly angioinvasive infiltrate of mostly medium-sized lymphoid cells within the walls of veins and small arterioles in the mid and deep dermis. In the majority of the biopsies, the infiltrates contained numerous eosinophils arranged interstitially or forming small clusters around blood vessels, which however were not found within the vessel walls like in leukocytoclastic vasculitides. Particularly in LyP type A, vasculitic changes may be observed, but to a much lesser extent than in our cases in which the angiocentric and angiodestructive growth pattern was the predominant one. The infiltration of the walls of dermal vessels (and sometimes subcutaneous vessels) of different size may also explain the clinical features with large ulcers, whereas in other LyP types, occasionally, only small and superficial ulcerations occur on the top of the papules and nodules before they begin to undergo spontaneous regression.

Some of our cases manifested infiltration of smooth muscle bundles and perineural spaces by lymphocytes which may impart a worrisome appearance, inasmuch as this feature is often observed in authentic lymphomas. However, in recent years it has become increasingly recognized that this feature can also be seen in benign lymphoid proliferations (pseudolymphomas). Parenthetically, the lesion in the above mentioned case of borderline CD30+ cutaneous lymphoproliferative disorder displayed this feature as well. (54) , (7), (10), (29)

A further potentially worrisome finding in our cases was the presence of a dominant T-cell clone in more than half of the examined biopsies. Detection of clonal T-cells in LyP varies from 20 to 80% and differs significantly among the various histopathologic forms of LyP. (22).

There are only very few reports on LyP cases with an angiocentric pattern, mostly presented as case reports. (69), (44), (9), (3), (23), (25) Generally, they differ from our patients by the clinical features of multiple recurrent papular lesions, whereas our patients did show few hemorrhagic, partly self-healing ulcerations. A single small series of 5 LyP cases with CD8-positive cells was reported by Magro and coworkers. (44) Four of their 5 cases were consistent with classic LyP, whereas the fifth case could be identified by the authors as primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma. (44).

The angiocentric infiltrates in LyP in our series displayed mostly a CD8+ cytotoxic phenotype without loss of CD2 or CD5, but there was a slight variation with respect to expression of CD3 and CD7 (Table 2). In some cases however in addition to CD8 perivascular and intramural cells there were lymphoid cells expressing CD4, but cells with cytotoxic phenotype dominated in the angiocentric infiltrates. Remarkably, in some cases in which only few atypical lymphocytes expressed CD8, they were immunoreactive for TIA-1. In one case, atypical lymphoid cells were CD56 positive. The expression of CD56 by angiocentric infiltrates of LyP has so far been only once. (69) Expression of CD56 by the CD30 positive lymphoid cells is a rare finding in LyP in general and is not associated with impaired prognosis. (6), (32)

The histological findings of angiocentric and angiodestructive infiltrates of atypical lymphocytes and their cytotoxic CD8+ phenotype in most cases of LyP type E may result in interpretation these cases as highly malignant and aggressive lymphomas. (13), (19) , (39), (47) , (50), (42), (45) , (52) , (62) In regard to the low-malignant course with the proclivity of the lesions to undergo spontaneous regression and the excellent prognosis, it is crucial to differentiate this LyP variant from primary cutaneous lymphomas with angiocentric infiltrates and/or a cytotoxic CD8+ or CD56+ phenotype. In the majority of cytotoxic CD8-positive cutaneous T-cell lymphomas, the course of the disease is characterized by rapid progression with cutaneous and visceral spread and fatal outcome within months to few years. (63), (59) The course of the disease in our patients does not correspond to the aggressive course observed in most cases of cytotoxic lymphomas. (1), (2), (9) Although all our patients experienced recurrences, in none of the patients did the disease progressed as to involve extracutaneous sites or caused death.

The differential diagnoses of LyP type E includes extranodal T/NK cell lymphoma, nasal type, cutaneous gamma/delta-positive T-cell lymphoma, adult T-cell leukemia/lymphoma, primary cutaneous as well as systemic anaplastic large-cell lymphoma. Extranodal T/NK cell lymphoma, nasal type is an aggressive lymphoma with angiocentric and angiodestructive infiltrates of CD3epsilon+, CD8+/-, CD56+ and necrosis, but in contrast to LyP type E, tumor cells usually lack expression of CD30. (20) , (33), (34) A subset of atypical cells express CD30 in extranodal NK/T-cell lymphoma nasal type and in other T-cell or NK-cell tumors but it is rarely expressed by *the majority* of atypical cells in these neoplasms. Moreover, extranodal NK/T-cell lymphoma, nasal type, is linked to EBV in virtually all cases, whereas none of LyP type E cases was

associated with EBV as demonstrated by the absence of EBV assessed by in situ hybridization (EBER) and PCR for EBV DNA, respectively. (56), (55) Finally, extranodal NK/T-cell lymphoma, nasal type, spreads to extracutaneous sites and has a poor prognosis. (4) Cutaneous gamma/delta lymphomas, which may present with angiocentric or subcutaneous infiltrates and ulcers, exhibit a poor prognosis, by definition have to express the gamma/delta chain of the T-cell receptor (TCR delta+) and lack the expression of beta-F1 (alpha/beta chain of T-cell receptor). (8), (26) In our series of LyP type E, atypical lymphoid cells in all cases stained for this marker expressed beta-F1 and were negative for TCR gamma/delta thereby excluding cutaneous gamma/delta lymphoma. Other cytotoxic lymphomas such as primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma is an highly aggressive lymphoma with expression of CD8+ epidermotropic infiltrates with numerous necrotic keratinocytes, but does not exhibit angiocentric infiltrates and is consistently CD30-negative. (9) Subcutaneous panniculitis-like T-cell lymphoma and adult T-cell lymphoma/leukemia are excluded as differential diagnosis based on clinical and/or histologic as well as immunophenotypic findings as well as association with HTLV-1. (21), (37) , (36), (41) , (46), (43), (49) , (53), (58), (60), (65), (68) Secondary cutaneous infiltrates of systemic ALCL were excluded by negative staging examinations.

Another differential diagnostic consideration for cases with mucosal involvement is a recently proposed condition, the so-called mucosal CD30-positive lymphoproliferation of the head and neck which may display a cytotoxic phenotype. (61) Involvement of oral mucosa and lips were much more common in our series than it has been reported in other LyP variants, in which the occurrence of oral LyP lesions is exceedingly rare. In one patient in our series, the diseases started with oral mucosa involvement, while there were no skin lesions.

Like all LyP types, LyP type E shares features with primary cutaneous anaplastic large-cell lymphoma, in which rarely angiocentric infiltrates and CD8+ phenotypes have been reported. (15), (48), (70) This is probably the most challenging differential diagnosis as only a few or even a solitary lesion may be present at a given time, thus seriously limiting application of the general clue of multiples lesions in LyP versus a solitary lesion in ALCL to the distinction between these two forms of CD30+ lymphoproliferative disorders of the skin. The recurrent lesions are in favor for LyP in our series but this feature may require follow-up. The overlapping features between LyP and PCALCL, however, is emphasized by their categorization as part of the spectrum of CD30+ LPD. (27), (28)

The majority of the patients were treated by UV light therapy or topical antiseptics and topical steroids. Low dose methotrexate to control disease was used in only three patients, Irrespective of the treatment modality used, more than half of the patients experienced complete remission after a median follow-up of 3 years. None of the patients in our series developed a second lymphoid neoplasm as it has been reported to occur in up to 25% of LyP patients and none of the patients had died due to the disease. (17) , (67), (51), (64)

In conclusion, we describe a clinically and histologically rare, but unique form of LyP clinically characterized by occurrence of a few nodular or papular lesions that rapidly ulcerate and appear as hemorrhagic eschar-like ulcers. Histopathologically, a hallmark of the disease is an angioinvasive infiltrate of small to large atypical lymphoid cells with chromatin-dense or moderately chromatin-dense pleomorphic nuclei and expression of CD30 as well as cytotoxic markers such as CD8 and TIA-1 and necrosis due to destruction of infiltrated vessels. A dominant T-cell clone is found in a majority of the cases. The disease follows an indolent course, have an excellent prognosis, with the lesions manifesting tendency for spontaneous regression and recurrences, a characteristic feature of other forms of LyP, for which we propose a designation LyP, type E. This LyP type clinically differs from other classic LyP variants by the absence of multiple papulo-nodular lesions, though few papules similar to those in classic LyP can be observed in rare patients at one point of the disease, thereby indicating the link between this rare form of LyP and its other more common variants. On the other hand, the oligolesional manifestation or even occurrence a single lesion at a certain time point supports the current evidence that LyP and ALCL comprise a spectrum, with borderline lesions. LyP, type E differs from ALCL by angiocentric infiltrates CD30+ CD8+ atypical lymphocytes. Aggressive treatment such as multiagent chemotherapy and bone marrow transplantation, which is often employed in highly malignant angiocentric or cytotoxic lymphomas, should be avoided in LyP type E like in other forms of primary cutaneous CD30+ lymphoproliferative disease of the skin. (31) Excision, radiotherapy and UV-light therapy were efficient treatment modalities in our patients.

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Figure legends

Figure 1: Large ulcers (A, B) and scars (B, C) after preceding ulcerative lesions. (Case 2)

Figure 2: Large (2 cm) black (eschar-type) ulcer due to hemorrhagic necrosis on the foot. (Case 1)

Figure 3: In addition to two eschar-like ulcers on the trunk, few papules can be recognized in this patient. (Case 12)

Figure 4: Eschar-like ulcer on the face (A), healing with a scar (B). This patient experienced several recurrences on the face (C, D, E) and trunk (F). (Case 10)

Figure 5: Necrotic epidermis, dense angiocentric infiltrates in the dermis and subcutis, numerous thrombi and involvement of the subcutis can be recognized (A, B). Close-up view of the perivascular infiltrate with necrosis and erythrocyte extravasation (C) and pleomorphic cells infiltrating the vessel wall (D). Staining for CD30 (E) and CD8 (F) at scanning magnification and a close-up view demonstrating angiocentric infiltrates composed of CD30+ (G) and CD8+ (H) lymphocytes. (Case 1)

Figure 6: Atypical medium sized lymphocytes surrounding and infiltrating blood vessels (A, B). Rimming of atypical lymphoid cells around adipocytes (B). Staining for CD30 (C), CD4 (D), CD8 (E), and TIA-1 (F). Note the small number of CD8+ cells (E), whereas TIA-1 is expressed by most lymphocytes (F). (Case 6)

Figure 7: Marked epidermotropism of small to medium-sized atypical lymphocytes (A, B) co-expressing CD30 (C) and CD8 (D). (Case 11)

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Table 1: Clinical features, treatment and follow-up of the patients

Case	Sex/Age	Clinical features and course	Treatment	Follow-up (status, length)
1	M/74	First lesion in the oral cavity as an ulcer that healed within 10 days. Relapse on the upper lip (ulcer) in 4 years and in the next 2 years 6 relapses on the oral mucosa and 4 lesions on the skin (hip, perineum, foot). Since then, 1 relapse per year (feet, scrotum, oral cavity, nose), with papules becoming ulcers and spontaneous healing. One or two lesions at a given time. Scar formation.	Topical steroids	AWD 144 months
2	M/13	Few small papules rapidly ulcerating and healing spontaneously. Four relapses in the next 3 years with 2-3 lesions at a given time on leg and trunk. Scar formation.	UVBnb (also for recurrent lesions)	NED 46 months
3	M/60	One or two lesions (rapidly ulcerating nodules) at a given time, involving the left foot, with 2 relapses within 2 years. Scar formation.	UVBnb	NED 21 months
4	M/76	Lesions on the forearm. Four relapses in the next 4 years limited to the right forearm. Scar formation.	Surgical excision	NED 72 months
5	F/75	Lesions on the abdomen, including an ulcer. Spontaneous regression with scar formation. Relapse in 4 years as two 5cm plaques.	Unknown	AWD 48 months
6	M/77	Few pyogenic granuloma-like ulcers on the left thigh and groin, relapse within 2 years with a single similar lesion on the hand	Prednisone and MTX, surgical excision	AWD 24 months
7	F/40	Few papules progressing to ulcers on the lower leg and trunk. Scar formation.	Bath PUVA	NED 5 months
8	M/37	Vasculitis-like hemorrhagic lesions (six on the sole, two on the shoulder).	Heliotherapy, PUVA	AWD 12 months
9	M/70	Vasculitis-like hemorrhagic lesions progressing to ulcers around the knee. Relapses on the trunk.	No treatment	NED 33 months
10	M/62	Two ulcers (1cm) on the lip and nose, and relapse with ulcers on the eyelid and the back 2 as well as 6 years later.	Local antiseptics Surgical excision	NED 83 months

11	M/66	Ulcers and blisters on the hands. Two recurrences limited to the hands in the following 3 years (localized form).	Surgical excision	NED 60 months
12	M/8	Few papules and 2 ulcers on the trunk. Scar formation.	Topical steroids	AWD 3 months
13	F/45	Few papules turning into ulcers on the legs.	MTX	NED 7 months
14	M/48	Granuloma pyogenicum like ulcers on the abdomen and eye lid.	MTX	NED 6 months
15	F/66	Ulcers on the upper and lower lip, oral mucosa, tongue and cheek		AWD 24 months
16	M/42	Multiple papules evolving into ulcers on the trunk	n.a.	AWD 12 months

AWD: Alive with disease; MTX: Methotrexate (low dose); NED: No evidence of disease; UVBnb: Ultraviolett B narrow band light therapy.

Table 2: Histopathological features based on the study of 21 specimens

Histopathological features	**N/(%)**
Epidermal necrosis/ulceration	16/(76%)
Epidermal acanthosis	4/(19%)
Vacuolar alteration	4/(19%)
Ballooning keratinocytes	2/(10%)
Epidermotropism	9/(43%)
Prominent papillary dermal edema	9/(43%)
Dermal necrosis	15(68%)
Interstitial eosinophils	16/(71%)
Erythrocyte extravasation	16/(76%)
Thrombi	11/(52%)
Vasculitis changes	7/(33%)
Intramural atypical cells	20/(95%)
Folliculotropism	3/(14%)
Syringotropism	8/(38%)
Pilosebaceous unit necrosis	2/(10%)
Eccrine/apocrine unit necrosis	4/(19%)
Adipose tissue atypical lymphocyte infiltration	8/(38%)
Skeletal muscle atypical lymphocyte infiltration	3/(14%)
Peri- or intraneural atypical lymphocyte infiltration	3/(14%)

Table 3: Immunohistochemical and EBER in situ hybridization

Case	CD2	CD3	CD4	CD5	CD7	CD8	CD30	CD45RA	CD45RO	CD56	TIA	betaF1	TCR gamma /delta	EBER	ALK-1
1	+	+	-	+	+/-	+	+	-	+/-	-	+	+	-	-	-
2	+/-	+	+	+	-/+	+	+	-	-	-	-	+/-	-	-	-
3 =	+	+	+	+	+/-	+	+	-	-	-	+/-	+/-	-	-	-
4	+	+	-/+	+	-/+	+	+	-	+/-	+	+/-	+	-	-	-
5 =	+	-/+	-	+	+	+	+	-	+/-	-	+	+	-	-	-
6*	-/+	+	+	-/+	-	-/+	+	ND	+	-	+	+	ND	-	-
7	+	ND	+/-	ND	+	+	+	ND	ND	ND	ND	ND	ND	ND	-
8	+	ND	-/+	+	ND	+	+	-	ND	+/-	+	+	-	-	-
9*	ND	-	+	ND	ND	+/-	+	ND	ND	-	ND	ND	ND	ND	-
10	+	+	-/+	+	-	+	+	-	-	-/+-	ND	+	-	ND	-

11	+	-/+	-/+	+	-/+	+	+	ND	ND	-	+/-	+	ND	ND	-
12*	+	+	+	+	ND	-/+	+	-	-/+	ND	ND	+/-	-	ND	-
13=	+	+	+	+	+	+	+	ND	ND	ND	ND	+	ND	ND	-
14*	ND	+	+	ND	ND	-/+	ND	ND	ND	-	-/+	ND	ND	-	-
15	+	+	-/+	+	+/-	+	+	-	+/-	-	+	+	-	ND	-
16=	+	+	+	+	+	+	+	ND	ND	-	-	+	-	-	-

Indicated for each antibody is staining for *perivascular* and/or *intramural* lymphocytes.

In the first column, the sign * denotes cases with a general predominance of CD4 cells over CD8 cells in the *interstitial* infiltrate, whereas the sign = signifies cases with approximately equal numbers of *interstitial* CD4 and CD8 cells. In all other cases, CD8 cells predominated over CD4 lymphocytes.

Figure 1
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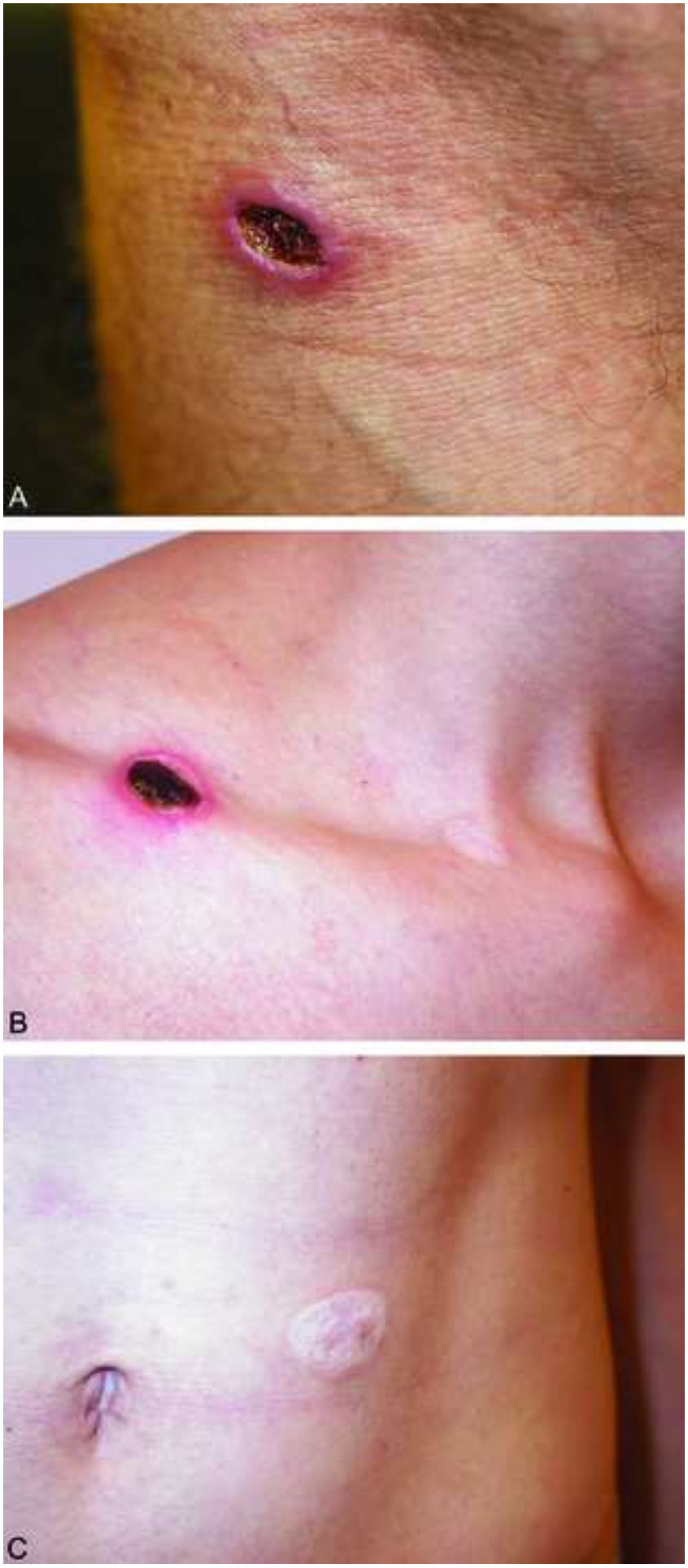

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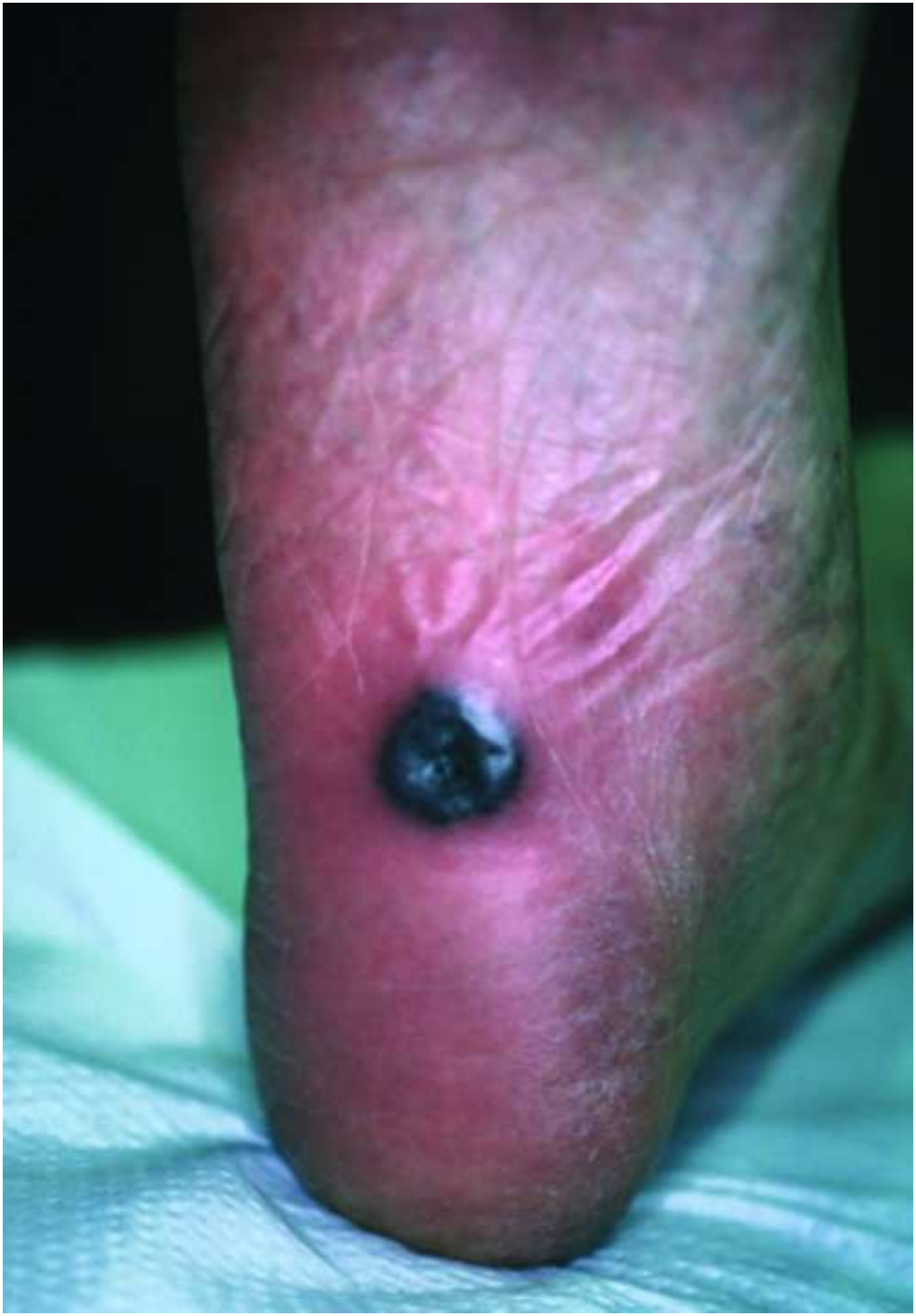

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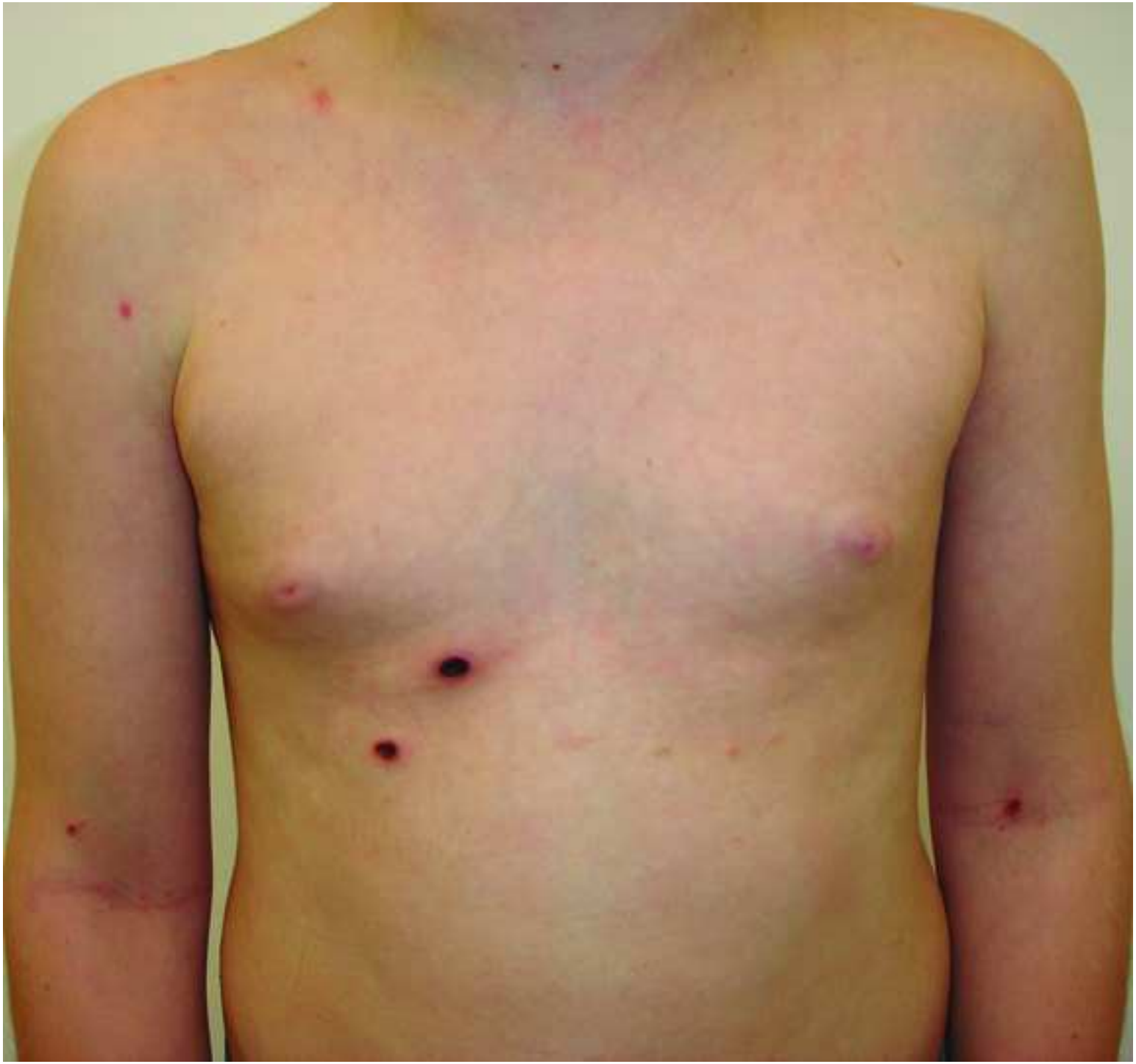

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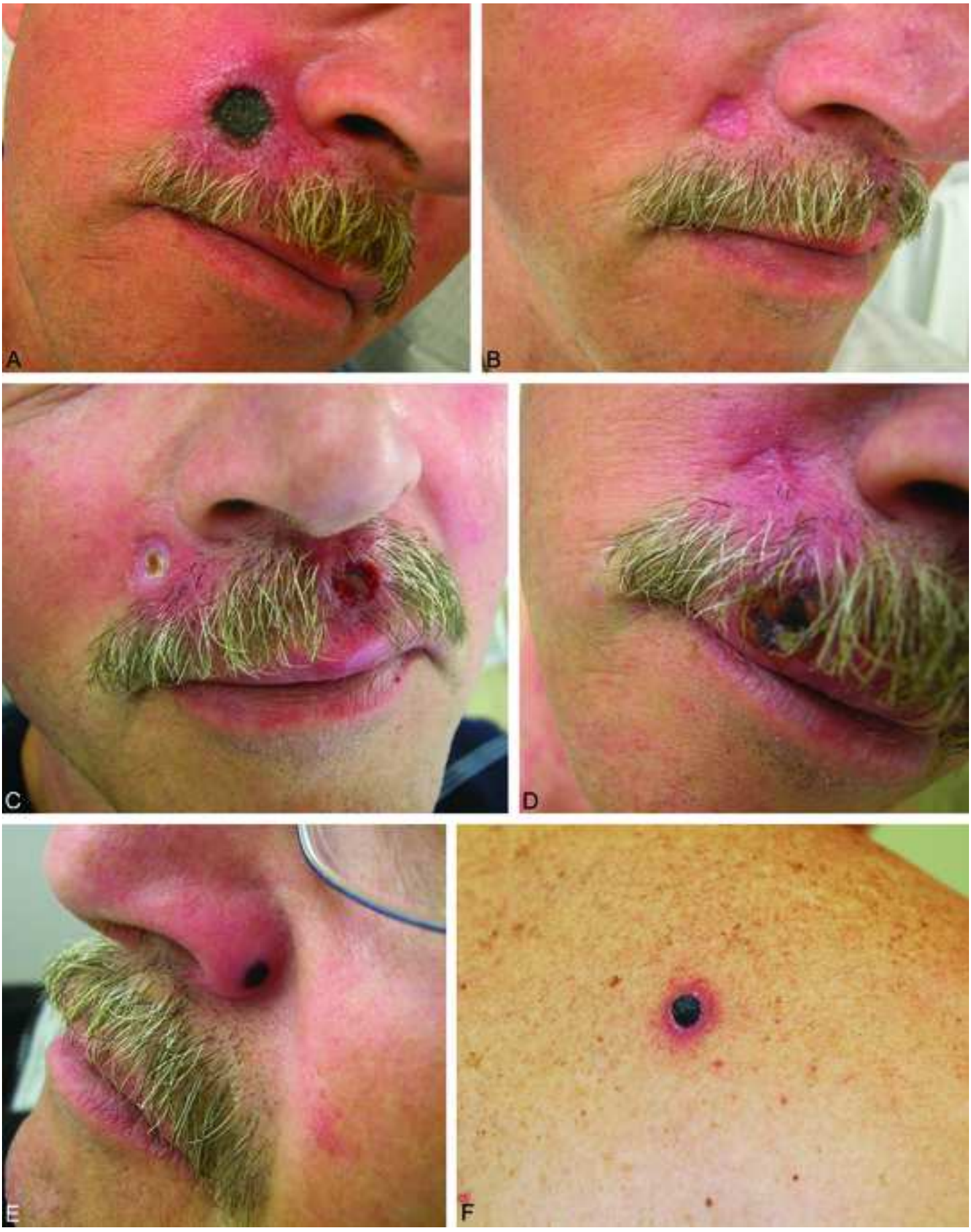

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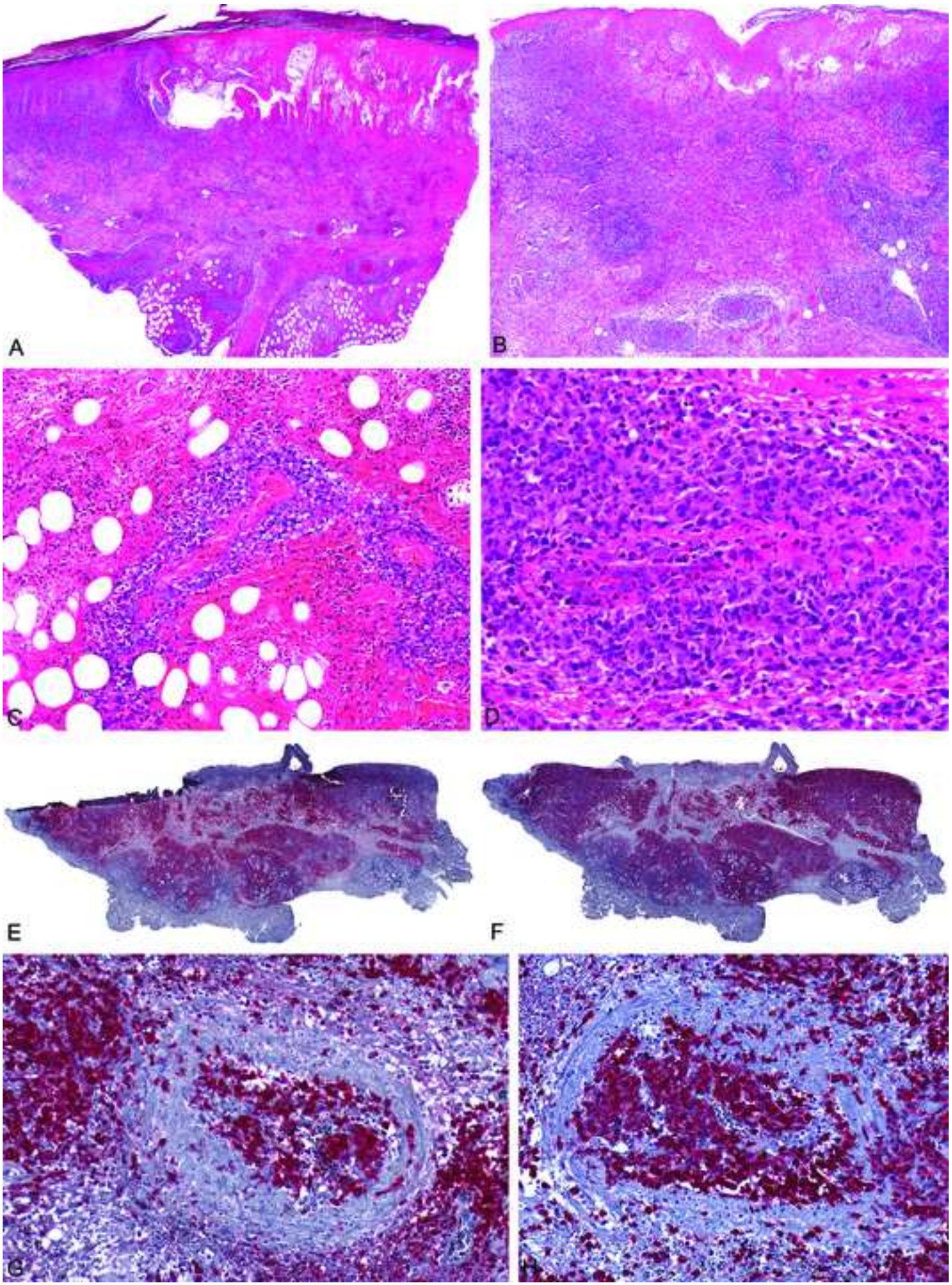

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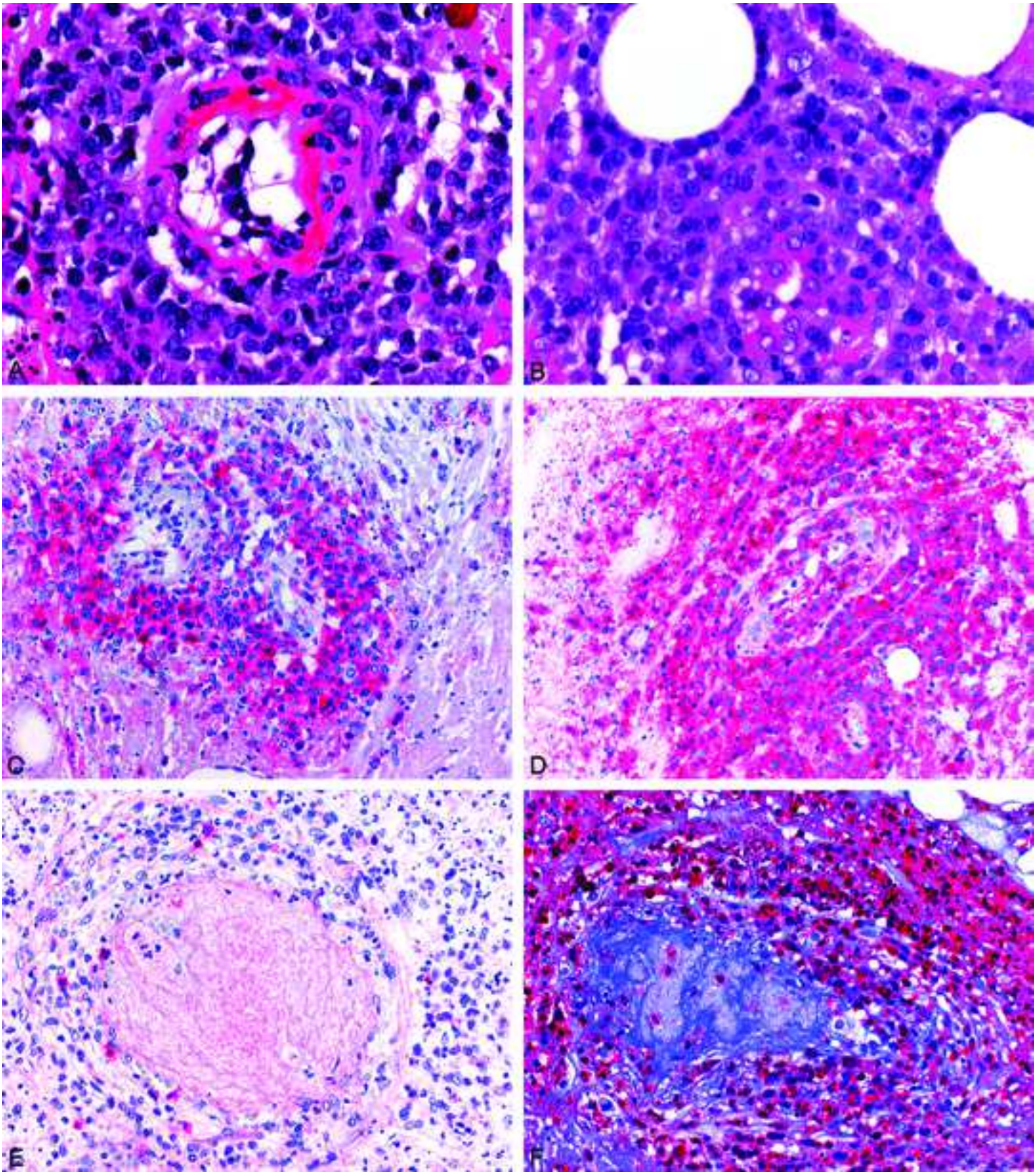

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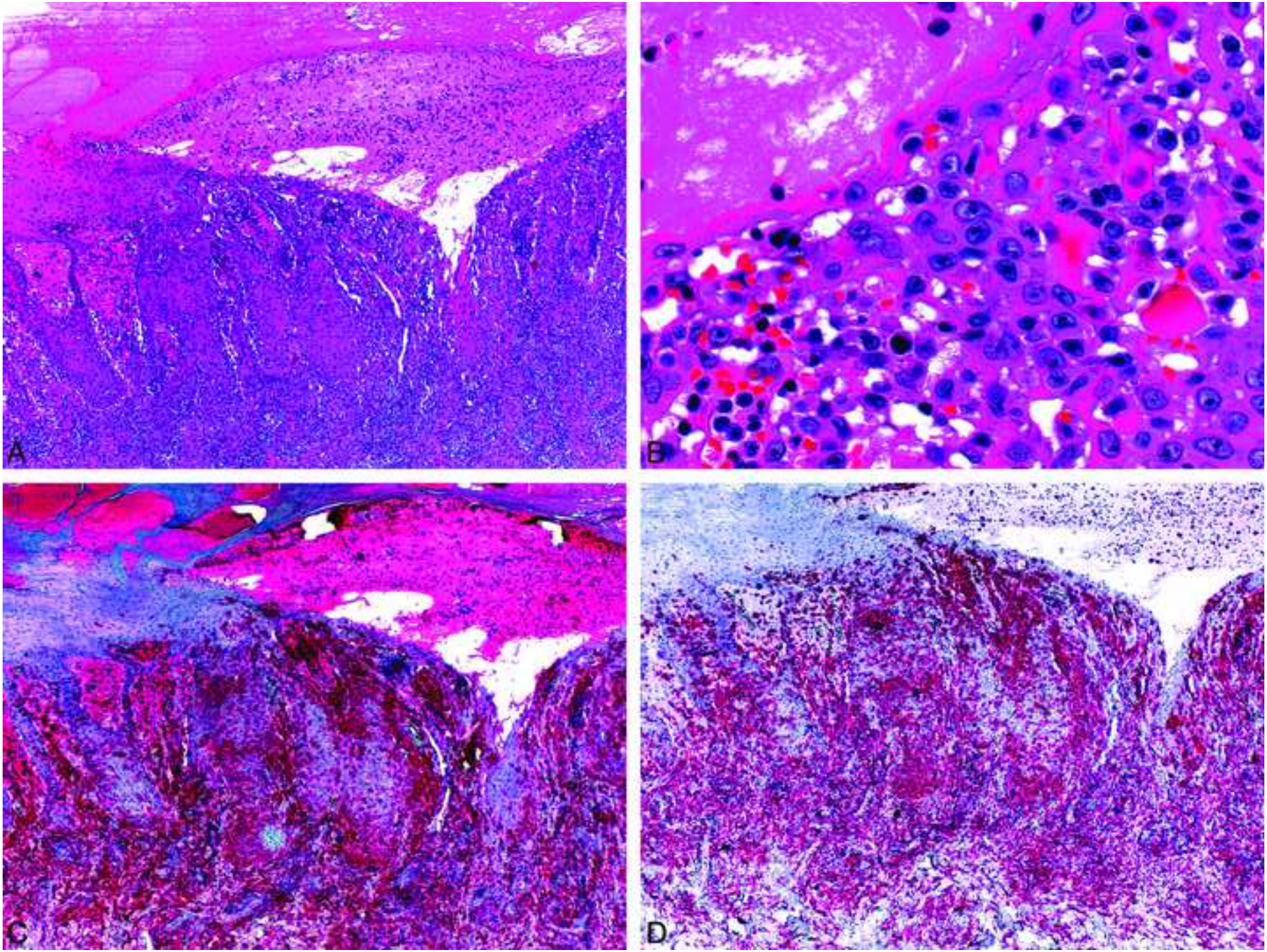

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