Supplementary Online Content

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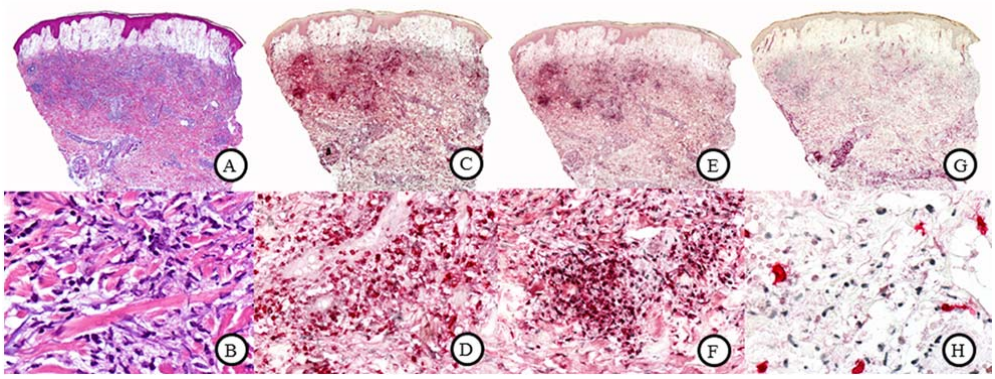
This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix

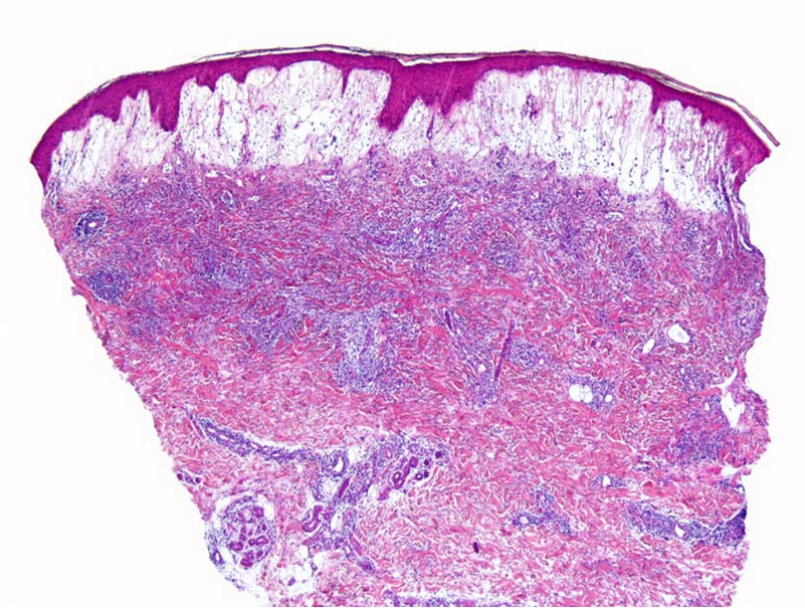
MATERIAL AND METHODS

For conventional light microscopy, skin biopsies were fixed in 4% formalin, embedded in paraffin, cut, and stained with hematoxylin-eosin. Automated immunostaining was performed on a BioTek Solutions Tech Mate (Tech-Mate 500; Biotech Solutions, Dako, Glostrup, Denmark). The antibodies used in this study targeted myeloperoxidase (MPO), CD163, MNDA, CD14, CD34 and CD117 (c-Kit). Their specificities and sources are given in eTable 1. To score the IHC results, we considered negative (-) , when no cells of the infiltrate were stained with the marker; +/-, when it was expressed by less than 10% of the cells of the infiltrate; +, when it was expressed by 10%-25% of the cells of the infiltrate; ++, when it was expressed by 25%–50% of the cells of the infiltrate; and +++, when it was expressed by 50% or more of the cells in the infiltrate. Double immunostaining was performed by combining pairs of the above mentioned antibodies and each marker was stained with a different color (black and red in each slide). We quantified the cell population that was positive for both markers and, in the same section, and also counted the positive cells for each marker individually. MNDA antibody stains nuclei of myelomonocytic cells, whereas the remainder antibodies mark cytoplasmic antigens.

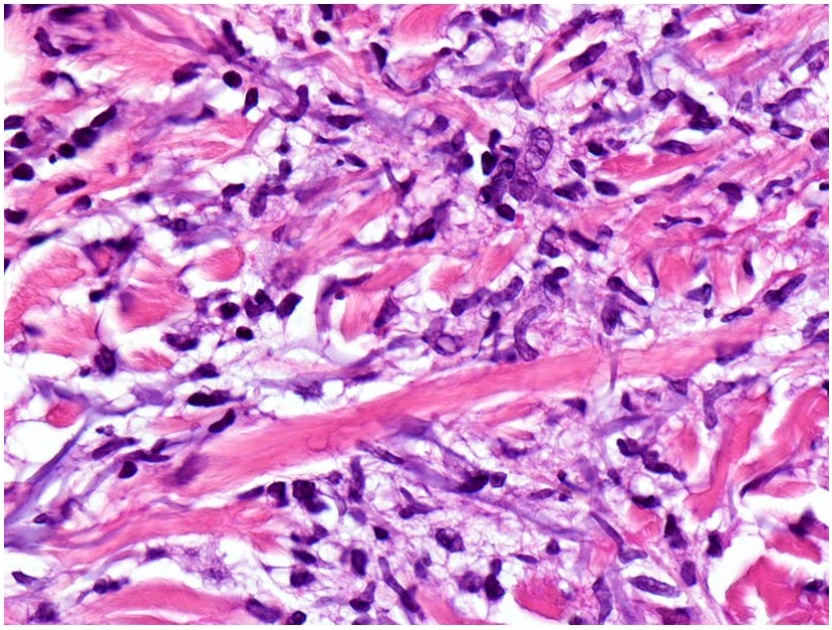
In 7 cases, fluorescent in situ hybridization (FISH) studies were performed on sections from paraffin-embedded tissue to rule out the presence of genetic abnormalities in the cells of the dermal infiltrate in the context of possible hematological disorder. For the detection of the *bcr/abl* translocation, a spectrum green and spectrum orange labeled probe was used (Abbott Diagnostics, Wiesbaden, Germany). Fluorescent in situ hybridization was performed as previously described.[1] In Case 33, interphase FISH study was performed in paraffin-embedded tissue from the patient. A probe to analyze region 5q was used following manufacturer recommendations (Abbot, Ill, USA). None of the cases of this study was included in the series reported in the original description of HSS.[1]



EFig. 1



EFig. 1A



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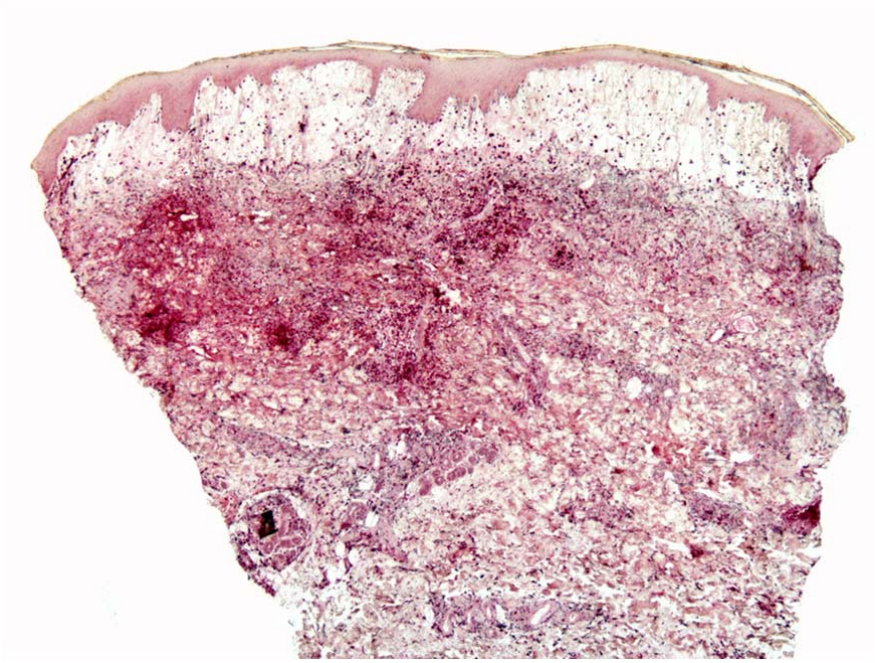
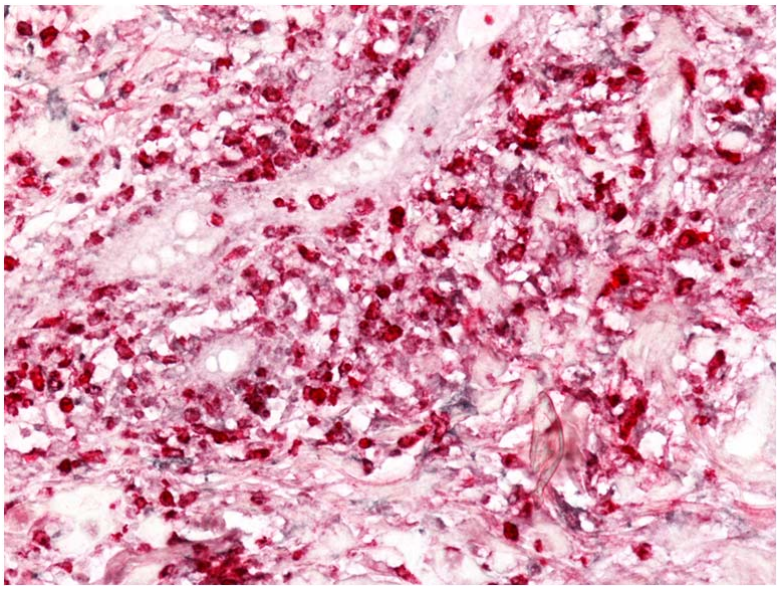


EFig. 1C



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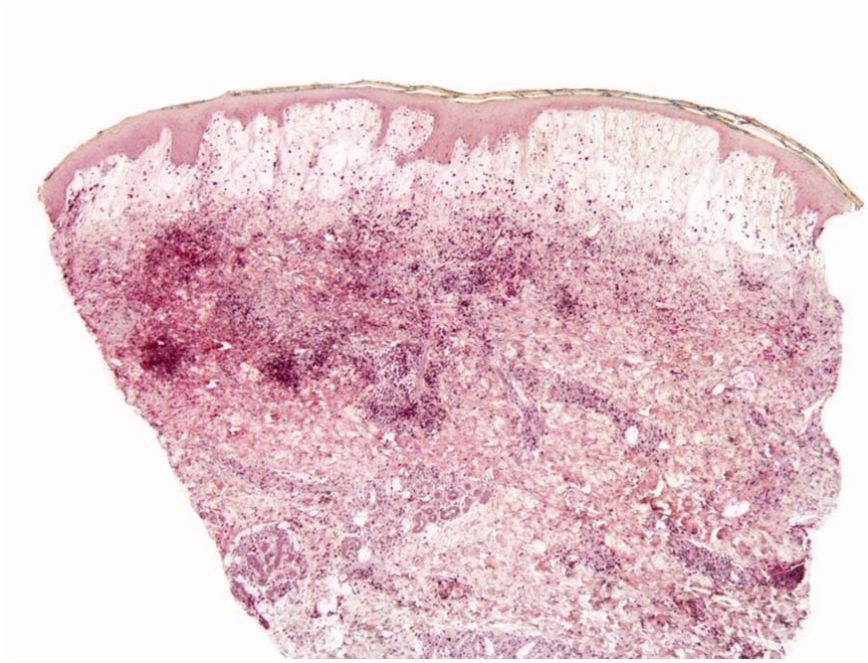

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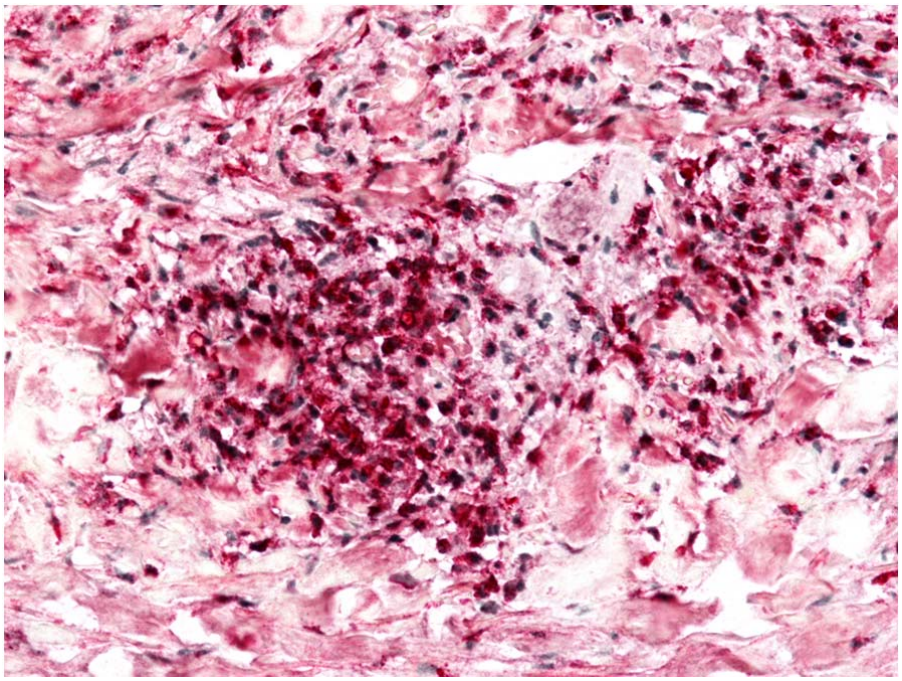

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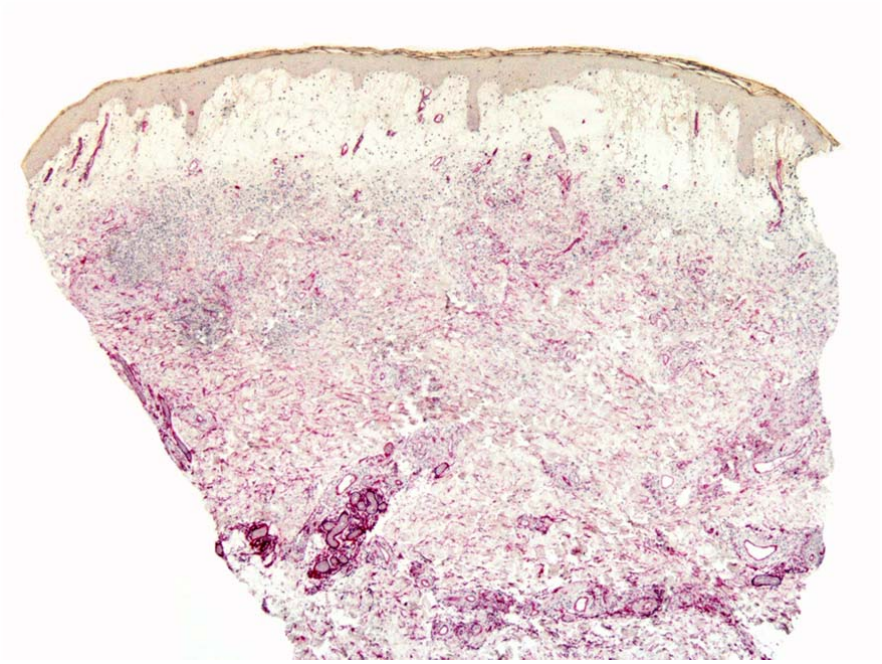

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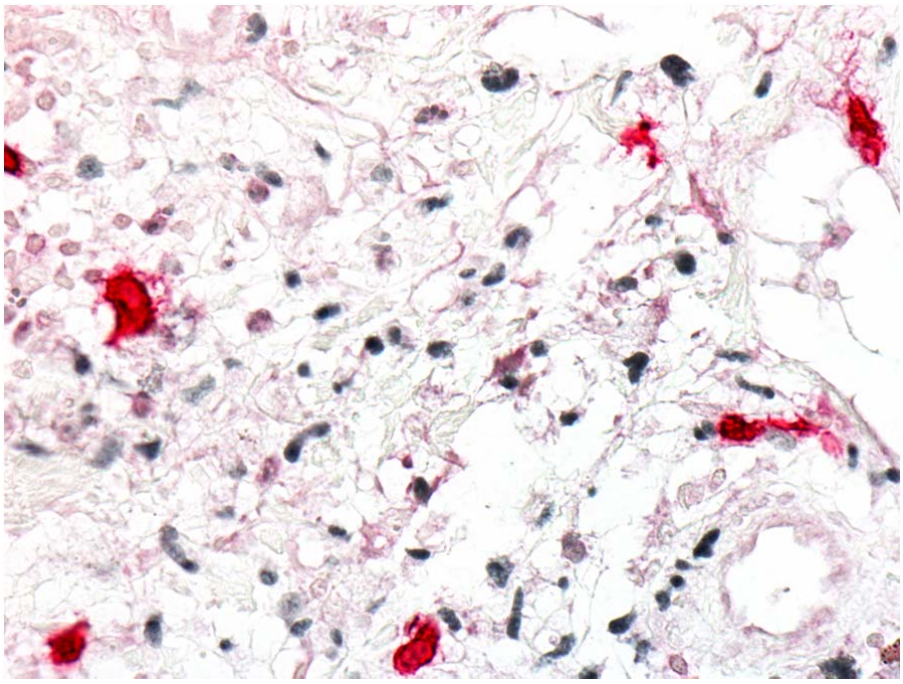

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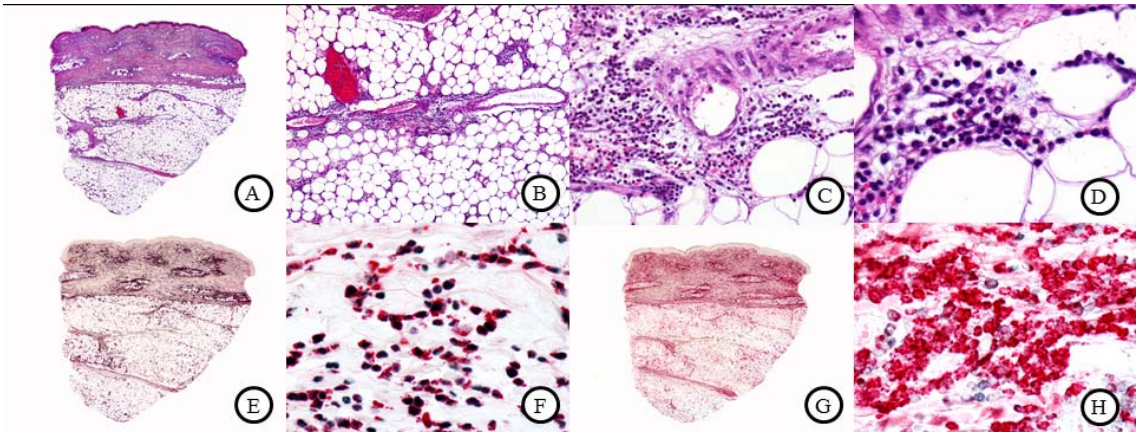
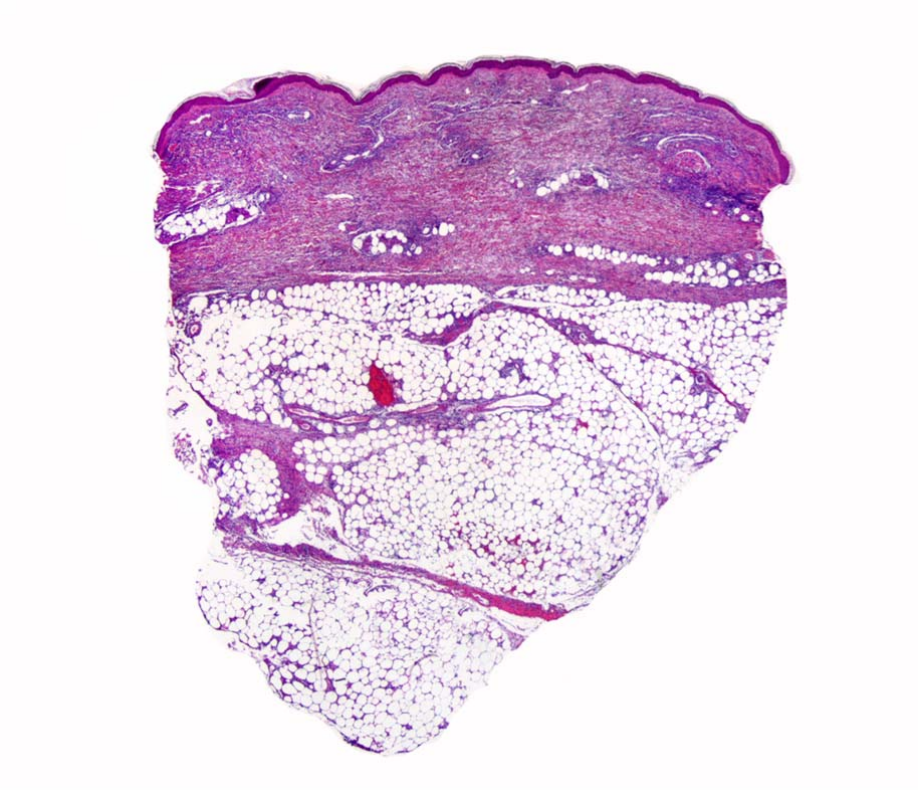
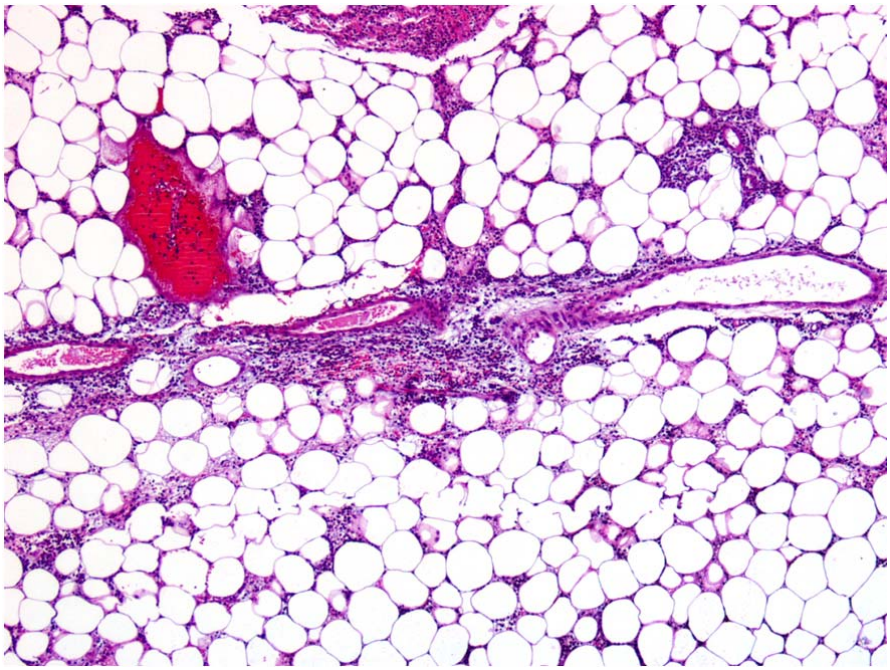


EFig. 2



EFig. 2A



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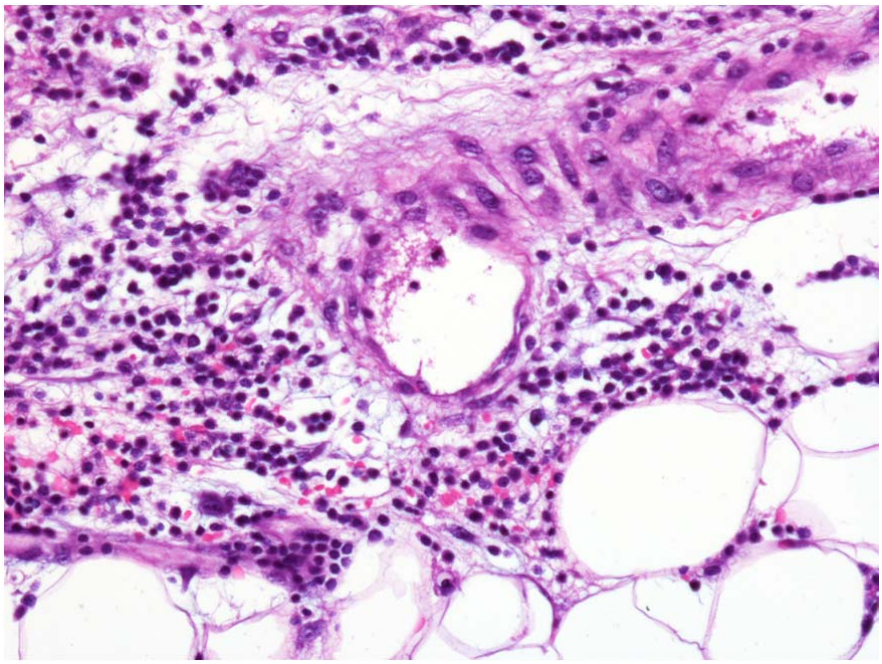

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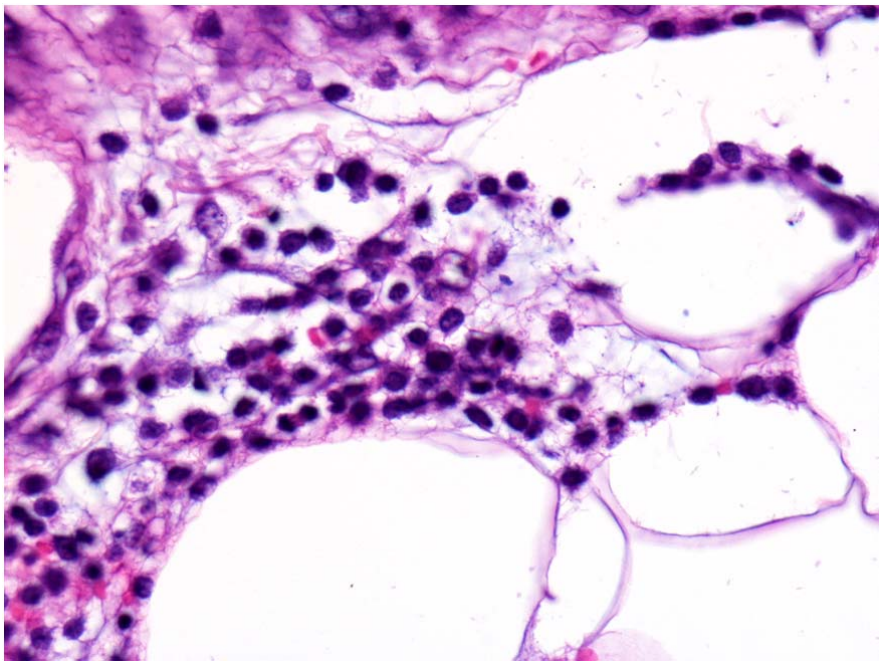
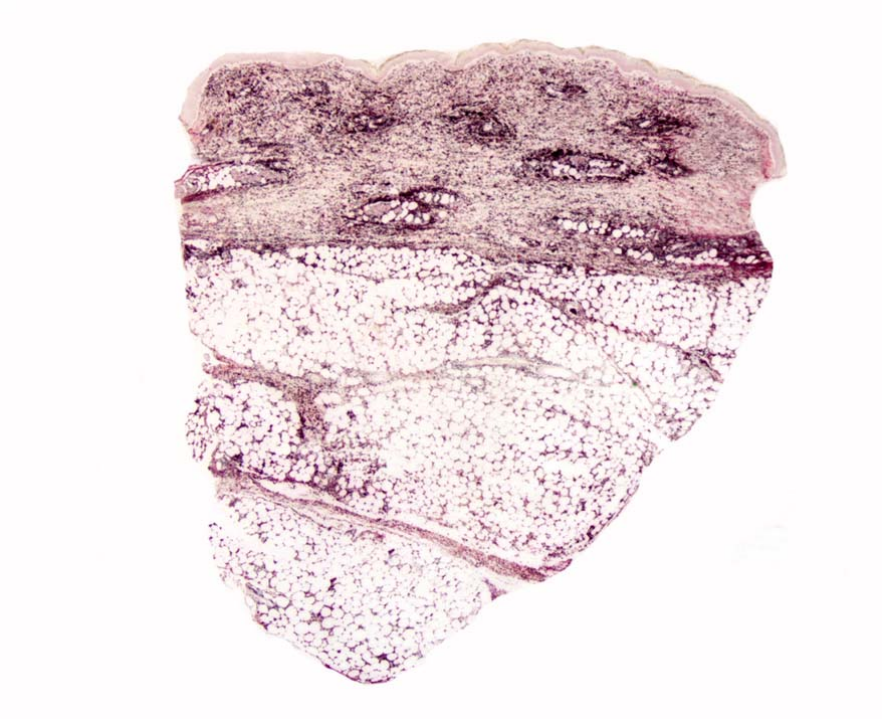


EFig. 2D



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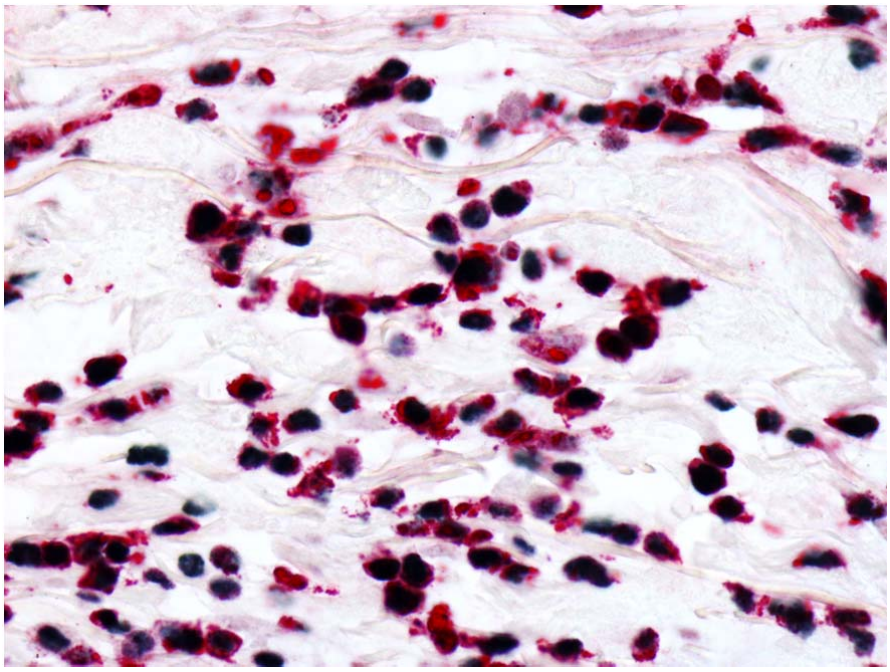

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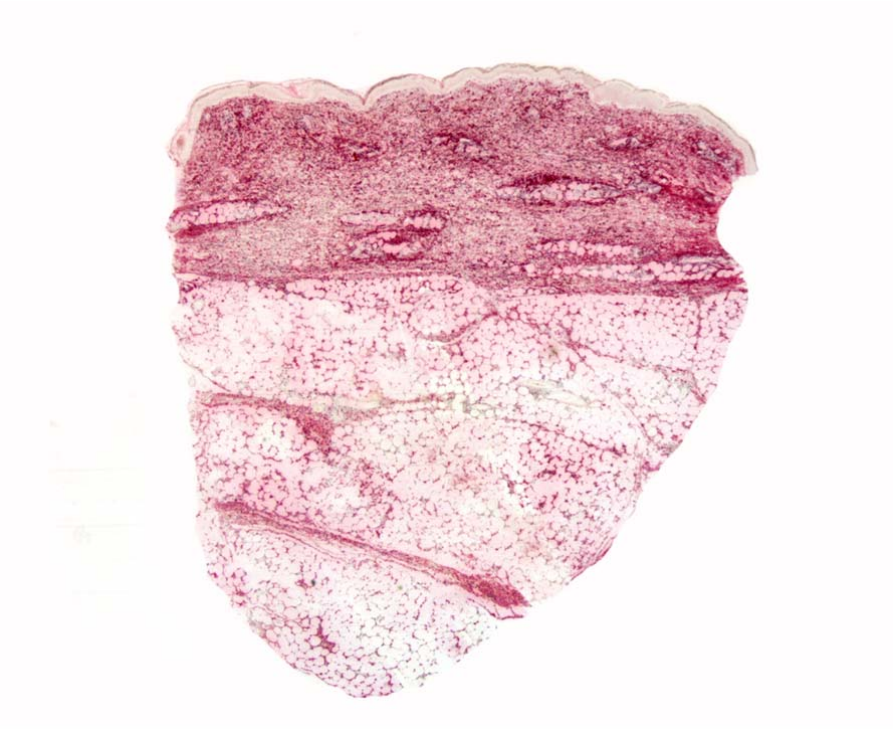
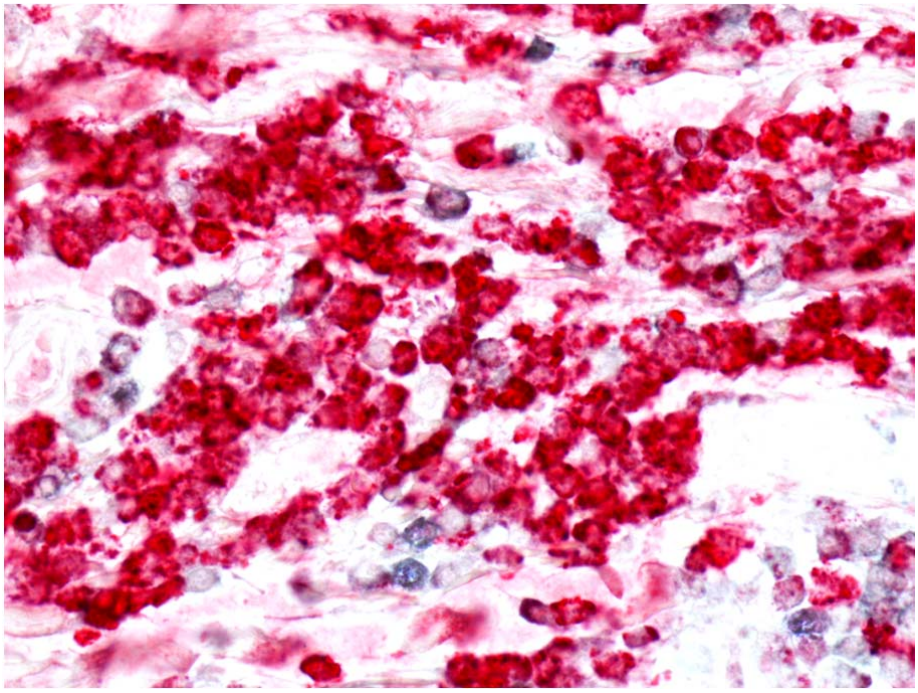


EFig. 2G



EFig. 2H

eFIGURE LEGENDS

EFig. 1. (Case 23). Histopathologic and immunohistochemical features of histiocytoid Sweet syndrome.

A. Prominent edema of the papillary dermis with dense dermal infiltrate. **B.** The predominant cells of the infiltrate were mononuclear cells with vesicular twisted nuclei and scant eosinophilic cytoplasm (Hematoxylin-eosin, original magnifications, A x20; B x400). **C.** Double immunostain with MPO (red color) and CD613 (black color). **D.** At higher magnification was evident that most cells expressed MPO (red color), but very few cells expressed CD163 (black color) (Double immunostain with MPO [red color] and CD163 [black color], original magnifications, C x20; D x200). **E**. Double immunostain with MPO (red color) and MNDA (black color). **F.** At higher magnification was evident that most cells co-expressed MPO in their cytoplasm (red color) and MNDA in their nuclei (black color) (Double immunostain with MPO [red color] and MNDA [black color], original magnifications, E x20; F x200). **G.** Double immunostain with CD163 (red color) and MNDA (black color). **H.** At higher magnification was evident that most cells expressed MNDA in their nuclei (black color), but very few cells expressed CD163 in their cytoplasm (red color). There were no cells co-expressing both markers (Double immunostain with CD163 [red color] and MNDA [black color], original magnifications, G x20; H x200).

EFig. 2 (Case 12). Histopathologic and immunohistochemical features of histiocytoid Sweet syndrome with subcutaneous involvement.

A. Scanning power showing dermal involvement and extension of the infiltrate into the subcutis. **B.** Higher magnification showing that the involvement of the subcutis was mostly septal. **C.** Most of the cells of the septal infiltrate are mononuclear cells. **D.** Still

higher magnification of the mononuclear cells of the infiltrate. (Hematoxylin-eosin, original magnifications, A x10; B, x100; C x200, D x400). **E.** Double immunostain for MPO (red color) and MNDA (black color). **F.** At higher magnification was evident that most cells of the infiltrate co-expressed MNDA in their nuclei (black color) and MPO in their cytoplasm (red color) (Double immunostain for MNDA [black color] and MPO [red color], original magnifications, E x10, F x400). **G.** Double immunostain for MPO (red color) and CD163 (black color). **H.** At higher magnification was evident that most cells expressed MPO (red color) and very few cells expressed CD163 (black color) (Double immunostain MPO [red color] and CD163 [black color], original magnifications, G x10, H x400).

eTable 1. Immunohistochemical markers used in this study

Monoclonal antibody	Clon and source	Dilution	Myeloblast	Promyelocyte	Myelocyte	Metamyelocyte	Neutrophil	Monoblast	Promonocyte	Monocyte	Histiocyte	Macrophage M2
CD34	my10, monoclonal mouse, Beckton-Dickinson, Heidelberg, Germany	1:100	++	-	-	-	-	+	-	-	-	
c-kit/CD117	Polyclonal rabbit, DAKO, Hamburg, Germany	1:100	+	+/-	-	-	-	+	-	-	-	-
Myeloperoxidase (MPO)	Polyclonal rabbit, DAKO, Hamburg, Germany	1:4000	+	++	++	++	++	-	+/-	+/-	-	+/-
CD163	10D6, Menarini, Berlin, Germany	1:2000	-	-	-	-	-	-	-	+/-	++	++
CD14	Polyclonal rabbit, EPR3653, Zytomed, Berlin, Germany	1:200	-	-	-	-	-	-	+	++	++	++
MNDA	Gift from Dr. Giovanna Roncador, National Cancer Research Center (NCRC), Madrid, Spain. Also commercially available from European Monoclonal Antibody Network [http://www.euromabnet.com/monoclonal-antibodies/mnda/21.html]	1:10	+/-	+	+	+	+	+/-	+	+	-	+/-

(-) Negative results; +/- (Weak positivity of few cells); + (Positivity of few cells); and ++ (Strong positivity of most cells). The red squares highlight the most probable immunophenotype of the predominant cell in histiocytoid Sweet syndrome.

e**Table 2. Clinical characteristics of this series of histiocytoid Sweet syndrome**

Case	Gender	Clinical presentation	Associated disorders/clinical outcome	Leukemia or other hematologic malignancy
1	F	Figurate erythema	Remission with imatinib	MDS, later CML (BCR-ABL +)
2	M	Waxing and waning tender papules and nodules mainly on the trunk	Recurrent for 3 years, still recurrent lesions 5 years later, under intermittent systemic steroids	No
3	M	Tender erythematous nodules on the extremities	Upper respiratory tract infection. Resolution	No
4	M	Tender nodules on the thigh and feet	None	MDS-RAEB, later NRAS- and monosomy 7- associated MDS-RAEB/AML
5	F	Papules and nodules on the face, extremities and trunk	No	No
6	M	Plaques on extremities	Ulcerative colitis, TNFalfa-induced polymyositis, elevated ANA	No
7	F	Plaques on buttocks, thighs and right breast	Hypertension, dyslipidemia, ictus, arthrosis, peripheral vascular disease, fibrocystic breast disease	No (BCR-ABL -)
8	F	Erythematous plaques on palms	Right breast intraductal carcinoma treated with surgery + RT + CT	AML
9	F	Plaques on lower extremities and trunk	Cardiovascular disease	No (BCR-ABL -)

Case	Gender	Clinical presentation	Associated disorders/clinical outcome	Leukemia or other hematologic malignancy
10	F	Plaques on lower extremities and palms	Hypertension and arthrosis	No (BCR-ABL -)
11	M	Plaques on extremities and trunk	Diabetes, tuberculosis, calcified meningioma	MDS (BCR-ABL -)
12	F	Plaques on extremities and trunk	Cardiovascular disease, renal disease and many others	MML
13	M	Tender plaques on the dorsum of the hands	Hypertension, asthma, hypothyroidism	PV, MDS later MML
14	M	Plaques on the dorsum of the hands	Crohn's disease	No
15	M	Plaques on upper extremities and trunk	Diabetes	MDS-RCMD
16	M	Tender plaques on arms	Bronchoalveolar carcinoma with mediastinal and pleural infiltration	No
17	M	Erythematous plaques on arms	Ulcerative colitis, diabetes, osteoporosis	No
18	F	Tender plaques on forehead	Betalactam allergy	No
19	M	Plaques on the arms	Chronic bronchitis	No
20	F	Erythematous plaques on back	Dyslipidemia	No
21	F	Plaques on the arms	Optic neuritis and idiopathic partial deficit of TSH, GH and ACTH	No

Case	Gender	Clinical presentation	Associated disorders/clinical outcome	Leukemia or other hematologic malignancy
22	F	Plaques on forehead	None	No
23	F	Erythematous plaques on head and neck	Puerperium	No
24	F	Plaques on back	Non-Hodgkin lymphoma, diagnosed 5 years later	No
25	F	Plaques on the back, elbows and face	Hypertension, heart disease, left bundle branch block	No
26	F	Plaques on the upper extremities and trunk	Dyslipidemia	No
27	M	Plaques on the upper extremities, face and trunk	None	MDS-RAEB
28	F	Plaques on the arms	Ulcerative colitis, hypothyroidism and metabolic syndrome	No
29	M	Plaques on the hands	Lung cancer, bladder cancer, hypertension, ischemic heart disease	No
30	F	NA	NA	No
31	F	Waxing and waning tender papule and nodules mainly on extremities	NA	No
32	F	4 years of waxing and waning lesions on buttocks, thighs, knees,	None	No

Case	Gender	Clinical presentation	Associated disorders/clinical outcome	Leukemia or other hematologic malignancy
32	F	elbows and hands		
33	F	4 years of waxing and waning lesions on upper and lower extremities, mainly hands	None	Monosomy of chromosomes 5 detected by FISH

MDS: Myelodysplastic syndrome; CML: Chronic myelogenous leukemia; AML: Acute myelocytic leukemia; RAEB: Refractory Anemia with Excess Blasts; RT: Radiotherapy; CT: Chemotherapy; MML: Myelomonocytic leukemia; PV: Polycythemia vera; RCMD: Refractory Cytopenia with Multilineage Dysplasia; NA: Not available.