# Diploma Thesis

## HISTOPATHOLOGIC DIAGNOSTIC CRITERIA FOR SPECIFIC MANIFESTATIONS OF MYELOGENOUS LEUKEMIA AND COMPARISON WITH INFLAMMATORY DERMATOSES AND BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM


presented by

**Marcela Martínez Escanamé y Pinales**


in order to obtain the degree

**Doktorin der gesamten Heilkunde**

**Dr. med. univ.**

at

**Medizinische Universität Graz**

performed at

**Klinik für Dermatologie und Venerologie**

under supervision of

**Univ. Prof. Dr. med. Lorenzo Cerroni**

Graz, June 24th 2015

*Eidesstattliche Erklärung*

*Ich erkläre ehrenwörtlich, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe verfasst habe, andere als die angegebenen Quellen nicht verwendet habe und die den benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe.*

*Graz, am 24. Juni 2015* *Marcela Martínez Escanamé y Pinales e.h.*

## Acknowledgement

I would like to express my sincere gratitude to my advisor Professor Lorenzo Cerroni for the unconditional support in my Thesis, for his patience, motivation, enthusiasm, and immense knowledge. His guidance helped me in all the time of research and writing of this thesis. I could not have imagined having a better advisor and mentor for my thesis respectively study.

Besides my advisor, I would like to thank Dr. Isabella Fried for her support, suggestions and friendship.

I also would like to thank all people who worked in the dermatopathology laboratory of the Department of Dermatology, Medical University of Graz: My research would not have been possible without their help.

Finally, I would like to thank my husband Marco and my son Mateo. They always have been there cheering me up and assisting me in the good and bad times.

# Table of Contents

# List of Tables

# List of Pictures

# Glossary and Acronyms

| | |
|---|---|
| AML | Acute Myelogenous Leukemia |
| BM | Bone marrow |
| BPDCN | Blastic Plasmocytoid Dendritic Cell Neoplasm |
| CML | Chronic Myelogenous Leukemia |
| GA | Granuloma Annulare |
| LC | Leukemia Cutis |
| ML | Myelogenous Leukemia |
| MPO | Myeloperoxidase |
| NaSDCl | Naphthol AS-D chloroacetate esterase |
| WHO | World Health Organization |

# Zusammenfassung

**Ziel:** Histopathologische und immunphänotypische Kriterien für die Routinediagnostik von spezifischen kutanen Infiltraten der myeloischen Leukämie (ML) zu etablieren, die insbesondere eine Abgrenzung zu malignen und benignen Erkrankungen mit ähnlichen morphologischen Merkmalen ermöglichen.

**Einleitung:** Die Diagnose spezifischer kutaner Manifestationen einer ML ist oft schwierig und in manchen Fällen kann eine entzündliche Dermatose durch ein myeloisches Infiltrat imitiert werden. Aufgrund der schlechten Prognose und hohen Notwendigkeit einer raschen Therapieeinleitung ist eine korrekte Diagnose der kutanen ML ausschlaggebend. In diesem Zusammenhang ist die differentialdiagnostische Abgrenzung von benignen Erkrankungen sowie von anderen hämatologischen Erkrankungen wie der blastären plasmazytoiden dendritischen Zellneoplasie (BPDCN) von höchster Bedeutung.

**Material und Methoden:** Es wurden Biopsien von 48 Patienten mit bestätigter kutaner ML ausgewählt. In Fällen mit ausreichend vorhandenem Material wurden immunhistochemische Färbungen unter Verwendung eines Antikörper-Panels für myeloische und lymphatische Zellen, sowie Färbungen für Naphtol AS-D Chloracentatereterase (NaSDCl) durchgeführt. Zur Evaluation differentialdiagnostischer Marker wurden die Biopsien der kutanen ML mit Biopsien von 33 bereits charakterisierten BPDCN Patienten verglichen. Außerdem erfolgte die Korrelation der Fälle kutaner ML mit 10 bereits charakterisierten Fällen von pseudolymphomatösem Granuloma anulare (GA).

**Ergebnisse:** Unter Berücksichtigung des klinischen und histopathologischen Bildes konnten zwei Hauptmuster bei kutanen Infiltraten einer ML beobachtet werden. Das erste Muster ist aus klinischer Sicht durch eine Vielzahl an Knoten und Plaques sowie histopathologisch durch dichtgelagerte diffuse Infiltrate von atypischen myelomonozytären Zellen in der gesamten Dermis gekennzeichnet. Das zweite Muster zeigt klinisch Merkmale einer entzündlichen Dermatose und histopathologisch relativ spärliche Infiltrate neoplastischer Zellen in der Dermis. Immunhistopathologische Färbungen zeigten bei beiden Mustern vergleichbare

Merkmale und waren in der Mehrheit der Fälle durch eine positive Reaktivität der Marker CD43, CD4, CD68, MPO und NaSDCI gekennzeichnet. Andere getestete Marker wie CD33, CD56, CD34, CD117, CD123, CD13 und CD1a waren nur bei einer geringen Anzahl an Proben positiv.

**Diskussion:** Die Studie zeigt, dass spezifische kutane Manifestationen einer ML unterschiedliche Muster aufzeigen können, wobei eines davon sehr schwierig von entzündlichen Dermatosen abgrenzbar ist. Einige Antikörper, insbesondere MPO, CD123, CD56 und in gewissem Ausmaße CD68, erwiesen sich bei der Differenzierung der ML von der BPDCN als hilfreich. Die Abgrenzung der kutanen ML von entzündlichen Dermatosen und insbesondere vom pseudolymphomatösen GA beruht auf sorgsamer Prüfung der histopathologischen Merkmale und der Verwendung eines Antikörper-Panels. Eine genaue Korrelation morphologischer und phänotypischer Merkmale zusammen mit dem Bewusstmachen dieser Entität, ermöglichen die korrekte Diagnose und Klassifizierung der kutanen ML sowie in weiterer Folge die adäquate Behandlung betroffener Patienten.

# Abstract

**Objetive:** Establish reproducible histological and immunophenotypic criteria for routine histopathologic diagnosis of cutaneous manifestations of myelogenous leukemia (ML), and for differential diagnosis from other malignant and benign cutaneous disorders showing similar morphologic features.

**Introduction:** The diagnosis of specific cutaneous manifestations of ML is often difficult, and in some instances skin lesions may mimic inflammatory dermatoses. A precise diagnosis is very important because of the poor prognosis and the need to start adequate therapy as soon as possible. In this context, the differential diagnostic demarcation from benign conditions as well as from other hematological diseases such as blastic plasmacytoid dendritic cell neoplasm (BPDCN) is paramount.

**Material and Methods:** We retrieved biopsies from 48 patients with a confirmed diagnosis of cutaneous ML. In cases with sufficient material, immunohistochemical stainings using a panel of antibodies for myelogenous and lymphatic cells as well as staining for naphthol chloroacetate esterase (NASDCl) were performed. In order to differentiate cutaneous ML from skin manifestations of BPDCN, histopathological and immunohistochemical results of biopsies from patients with cutaneous ML were compared with biopsies of 33 patients with proved diagnosis of BPDCN, which had been previously characterized. We also included for comparison 10 cases of pseudolymphomatous granuloma annulare (GA) which had also been previously characterized.

**Results:** Clinically and histopathologically, two main patterns of skin infiltrates of ML were observed. One was characterized clinically by multiple nodules and plaques and histopathologically by dense, diffuse infiltrates of atypical myelomonocytic cells within the entire dermis, whereas the second presented with clinical features similar to those of inflammatory dermatoses, and histopathologically by relatively sparse dermal infiltrates of neoplastic cells. Immunohistochemical stainings revealed in both patterns similar features, characterized in the majority of cases by positivity for CD43, CD4, CD68, MPO,

and NaSDCl. Other markers tested as CD33, CD56, CD34, CD117, CD123, CD13 and CD1a were positive only in a minority of specimens.

**Discussion:** Our study shows that specific cutaneous manifestations of ML may present with different patterns, one of which is very difficult to distinguish from inflammatory dermatoses. Some antibodies proved useful in the distinction of ML from BPDCN, particularly MPO, CD123, CD56 and to a certain extent CD68. Distinction of cutaneous ML from inflammatory dermatosis and particularly from pseudolymphomatous GA rests upon careful examination of the histopathological features and application of a panel of antibodies. Accurate morphologic and phenotypic correlation together with a high index of suspicion are necessary for a precise diagnosis and classification of cutaneous ML, in order to allow a proper management of affected patients.

# 1 Introduction

The diagnosis of specific cutaneous manifestations of acute myelogenous leukemia (AML) is often difficult. A precise diagnosis is very important because of the poor prognosis and the need to start adequate therapy as soon as possible. In this context, the differential diagnostic demarcation from other hematological diseases such as blastic plasmacytoid dendritic cell neoplasm (BPDCN) on the one hand and from inflammatory skin diseases on the other is paramount.

The target of this work is to establish reproducible histological and immunophenotypic criteria for routine histopathologic diagnosis of cutaneous manifestations of myelogenous leukemia (ML).

## 1.1 Cutaneous Myelogenous Leukemia

ML are a spectrum of diseases encompassing chronic myeloproliferative diseases, myelodysplastic disorders, AML and related disorders [Cerroni 2014]. The World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues takes into consideration genetic features with clinical, histopathologic and phenotypic aspects [Swerdlow 2008]. Specific skin infiltrates may be seen in both AML and chronic myelogenous leukemia (CML); however, in this last they usually represent a progression of the disease to a more aggressive phase, thus in what follows in the context of cutaneous manifestations the term ML will be used to refer to both.

Leukemia cutis (LC) refers to the specific infiltration of the skin by neoplastic leukemic cells, most often in conjunction with systemic leukemia [Cronin 2009]. Many terms have been used to describe varying presentations of leukemia cutis. These include granulocytic sarcoma, myeloid sarcoma and chloroma among others [Cerroni 2014]. However, the term LC is not specific, as the skin may be the site of specific manifestations of other types of leukemia (e.g., B-cell chronic lymphocytic leukemia). Thus, we will avoid this non-specific terminology.

In the last years, many publications showed that a relationship between ML and BPDCN exists [Cerroni 2014]. As BPDCN presents often with cutaneous lesions, ML must be differentiated from BPDCN confined to the skin. This may require extensive immunohistochemical studies [Cronin 2009, Cota 2010].

### 1.1.1 Clinical features

Specific cutaneous infiltrates in patients with ML show variable clinical and histopathological features [Kaddu 1999; Chang 2003; Berger 1973; Desch 1993]. sometimes deviating from the conventional presentation characterized by localized or generalized papules, plaques, unusual clinical features such as solitary skin nodules, maculopapular eruptions clinically resembling drug or viral eruptions, vasculitis, or other inflammatory skin diseases. Involvement of mucosal regions is common [Cerroni 2014, Hsaio 2011].

The clinical differential diagnosis is broad, as a wide range of neoplastic, inflammatory and infectious skin lesions may be associated with hematologic malignancies and/or their treatment [Cronin 2009].

In rare cases, specific cutaneous infiltrates of ML represent the first clinical manifestation of the disease, preceding blood and/or bone marrow changes by weeks or even month. This is known as “aleukemic" leukemia cutis [Cerroni 2014, Hejmadi 2008, Kaddu 1999]. The patients should be managed in the same way as those with cutaneous manifestations of known ML [Cerroni 2014].

In some patients specific manifestations can be observed at the side of cutaneous inflammation, where circulating leukemic cells may be attracted to the skin by normal chemotactic stimuli [Diaz-Cascajo 1998]. This phenomenon has been reported in lesions of Sweet´s syndrome, psoriasis, basal cell carcinoma, needle puncture and infusion of gabexate mesilate that had leaked from the vein [Díaz-Casajo1998, Metzler 1997, Urano1999, Deguchi 1977].

### 1.1.2 Histopathological features

Histologically, the disposition of the neoplastic infiltrate in cutaneous ML can vary from mild or moderate to dense, diffuse or nodular dermal infiltrates, often with perivascular and periadnexal accentuation and sparing of the upper papillary dermis. Involvement of the subcutis is common [Cerroni 2014, Kaddu 1999].

Frequently prominent single files of neoplastic cells between collagen bundles can be observed ("Indian filing"), as well as a distinctive "figurate" pattern characterized by neoplastic cells arranged in concentric layers around blood vessels and adnexal structures [Cerroni 2014].

There can be variation in the cytologic appearance of the neoplastic cells, but the infiltrate is composed mostly of medium-sized, round to oval, mononuclear cells with a slightly eosinophilic cytoplasm and distinct, sometimes indented, bilobular or kidney-shaped basophilic nuclei [Kaddu 1999].

Variable numbers of mitotic figures, including atypical mitoses, and apoptotic cells can be found. In some cases, reactive inflammatory cells are present [Baksh 1998, Kaddu 1999, Tomasini 1998].

### 1.1.3 Immunophenotype

Immunohistochemical stains are often necessary to determine the origin of the neoplastic cells and to confirm a diagnosis of specific skin manifestations of ML [Kaiserling 1994, Sepp 1993].

Markers that are usually expressed by neoplastic cells in cutaneous ML include MPO, lysozyme, CD13, CD14, CD15, CD33, CD43, CD45, and CD68, but some cases may show positivity for only a few of these antigens [Cerroni 2014]. CD68 is the most sensitive (but not specific) monocitic antigen in cutaneous ML [Benet 2011, Cronin 2009, Kaddu 1999, Cibull 2008]. CD43 staining is consistently positive but is also present on T lymphocytes, thus it must be evaluated in conjunction with other T-cell markers [Seep 1993]. CD163 is a monocytic specific antigen but has a lower sensitivity and is expressed in about 40% of cases [Jefferey 2011, Garcia 2008].

Staining for naphtol-ASD-chloracetate-esterase (NASDC1, Leder stain) is positive mainly in cases with a more mature phenotype, but tends to be negative in more immature cells [Cerroni 2014].

Cutaneous lesions of ML are commonly positive for CD4, whereas markers like CD56 or CD123 are usually negative. On the other hand, in a minority of cases these two markers, too, may be positive, thus presenting overlapping features with cutaneous lesions of BPDCN, and rendering the differential diagnosis problematic [Kuwabara 1999, Kaddu 1999, Cota 2010, Cerroni 2014, Cibull 2008, Hejmadi 2008].

A proportion of neoplastic cells in some cases of cutaneous ML may be positive for S100 protein, thus representing a pitfall in the differential diagnosis with histiocytic disorders (e.g., Langerhans cell histiocytosis) if complete phenotypic analyses are not carried out [Cerroni 2014].

## 1.2 Blastic Plasmocytoid Dendritic Cell Neoplasm

BPDCN, formerly named CD4+/CD56+ hematodermic neoplasm, is a clinically aggressive tumor derived from the precursors of type II plasmacytoid dendritic cells, with a high frequency of cutaneous and bone marrow (BM) involvement and leukemic dissemination [Facchetti 2008]. The term BPDCN has been adopted by the new WHO classification of tumors of Hematopoietic and Lymphoid Tissues, and the entity is listed in the section on AML and related precursor neoplasms [Swerdlow 2008].

### 1.2.1 Clinical features

Most patients are elderly adults, but BPDCN can occur at any age, including newborns [Massone 2004, Jegalian 2010]. There is a predominance of males. Clinically, patients present with asymptomatic, solitary or multiple skin lesions that can be plaques or tumors. In some cases a characteristic "bruise-like" violaceous aspect due to intratumoral hemorrhage can be observed. Ulceration and mucosal involvement are uncommon [Julia 2013, Cerroni 2014].

In 30-40% of patients, cutaneous lesions are accompanied by general symptoms and extracutaneous manifestations in the blood, BM and/or other organs. Regional lymphadenopathy at presentation is common. Cytopenias are commonly found [Feuillard 2002].

Cutaneous involvement represents often the first manifestation of the disease, and primary cutaneous cases without overt leukemia represent examples of "aleukemic leukemia cutis". The time interval between the onset of skin lesions and leukemic dissemination is variable, usually between a few weeks and several months [Cerroni 2014, Julia 2013].

### 1.2.2 Histopathology

Histologically, BPDCN is characterized by a diffuse, monomorphous infiltrate of medium-sized neoplastic cells with a blastoid morphology. The epidermis is spared as a rule, whereas involvement of the subcutaneous tissues is common. Angiocentricity and/or angiodestruction, necrosis and granulomatous reactions are uncommon [Cerroni 2014].

### 1.2.3 Immunophenotype

Phenotypically, neoplastic cells in BPDCN are typically positive for CD4, CD56, CD123, TCL-1, and BDCA-2/CD303, and negative for specific myeloid, T-lymphoid, B-lymphoid, or NK-lymphoid lineage markers [Facchetti 2008, Cerroni 2014, Julia 2014, Cota 2010].

Any of the three cardinal markers for the diagnosis of BPDCN (CD4, CD56 and CD123) may be negative in given cases, and rarely more than one marker are not expressed by neoplastic cells [Cota 2010, Facchetti 2008, Argyrakos 2004, Julia 2014]. Diagnosis in such cases relies on broad panels of antibodies and careful histopathologic-phenotypic correlation. An important role in such cases is played by TCL-1, which is expressed by neoplastic cells in the majority of BPDCN [Herling 2003].

CD68 is positive in some cases of BPDCN [Julia 2014, Facchetti 2008, Petrella 2005]. In contrast to cutaneous lesions of ML, however, positivity is often granular and restricted to a subset of neoplastic cells [Cerroni 2014]. In a proportion of cases, neoplastic cells may express one or more other markers including CD2, CD7, CD45Ra, Bcl-2, CD43, CD101, BCL11A, CD2AP, and ICSBP/IRF8 [Cerroni 2014].

As already mentioned before, it is important to remember that cutaneous ML is also positive for CD4, and in some cases may be positive for CD56 and/or CD123. These markers should always be used together and in conjunction with a panel of antibodies directed toward lymphoid and myeloid lineages, and only integration of all stainings can allow a precise diagnosis [Cerroni 2014].

# 2 Material and Methods

The study has been conducted at the Research Unit Dermatopathology, Department of Dermatology, Medical University of Graz, Austria, and has been approved by the Ethic Committee of the University (EK-Nummer 21-080 ex 09/10).

## 2.1 Selection of cases

Files of the histopathological laboratory of the Department of Dermatology, Medical University of Graz were searched for skin specimens with diagnosis of cutaneous manifestations of ML. Cases with a confirmed diagnosis were selected. A total of 48 cases of skin manifestations of ML were included in the study. Data on some of these patients were published previously [Kaddu 1999, Martinez Escaname 2013].

In order to differentiate cutaneous ML from skin manifestations of BPDCN, we compared them with biopsies from 33 patients with a proven diagnosis of BPDCN that had been previously characterized at our Institution [Cota 2010].

Finally, we included for comparison also 10 cases of pseudolymphomatous granuloma annulare, a condition that because of the presence of pseudolymphomatous infiltrates and CD68+ cells may mimic specific skin manifestations of ML. These cases, too, had been characterized previously at our Institution [Cota 2012].

## 2.2 Histopathological and Immunohistochemical Studies

Specimens were stained with hematoxylin and eosin. More than one biopsy were available for some of the patients. In cases with sufficient material, immunohistochemical stainings using a panel of antibodies for myelogenous and lymphatic cells as well as staining for NASDCl were performed.

A standard immunoperoxidase technique with microwave enhancement was applied according to the manufacturers' protocols. Tonsil tissue and normal skin

structures served as external and internal controls, respectively. For negative controls, the primary antibody was omitted and replaced with normal human serum.

# 3 Results

## 3.1 Clinical data of the patients

Clinical data with a summary of provided clinical diagnoses are summarized in *Table 1*. There were 26 males and 22 females (M/F ratio = 1.2:1). The age ranged from 15 to 89 years (mean 56.6 years, median 59 years). A diagnosis of ML was known in 25 patients, whereas skin manifestations represented the first sign of the disease in 23 patients.

*Table 1: Clinical Data and Follow-up*

| Case No. | Gender/ Age | Provided Clinical Diagnosis | Clinical Findings | History of ML | Interval, Month | Follow-Up (Months) |
|---|---|---|---|---|---|---|
| **1** | M/81 | Leukocytoclastic vasculitis | Maculopapular eruption | Yes | 0 | D+(1) |
| **2** | M/62 | Hemorrhagic drug reaction | Maculopapular eruption | No | 18 | D+(32) |
| **3** | F/56 | Sweet syndrome | Edematous plaques | No | 1 | A+(19) |
| **4** | M/59 | Drug reaction | Maculopapular eruption | No | 0 | A+(25) |
| **5** | M/89 | Granuloma faciale | Plaques | No | 0 | A+(1) |
| **6** | F/24 | Eczema | Eczematous lesions | No | 3 | A+(14) |
| **7** | M/55 | Extramedullary hematopoiesis | Maculopapular eruption | Yes | 0 | D+(2) |
| **8** | M/81 | Psoriasis | Psoriatic plaques | No | 0 | A+(3) |
| **9** | F/31 | Drug reaction vs. virus eruption | Maculopapular eruption | No | 2 | A+(6) |
| **10** | M/63 | Drug reaction vs specific manifestations of ML | Maculopapular eruption | Yes | 0 | D+(26) |
| **11** | M/70 | Rule out specific manifestations of ML | Maculopapular eruption | Yes | 0 | D+(5) |
| **12** | M/72 | Drug reaction | Maculopapular eruption | Yes | 0 | A+(2) |
| **13** | F/15 | Drug reaction | Maculopapular eruption | No | 0 | A+(1) |
| **14** | F/27 | Drug reaction vs specific manifestations of ML | Maculopapular eruption | Yes | 0 | D+(15) |
| **15** | M/55 | Drug reaction | Maculopapular eruption | No | 1 | A+(5) |
| **16** | M/71 | Drug reaction | Maculopapular eruption | No | 0 | A+(1) |
| **17** | M/74 | Specific cutaneous manifestation of ML | Plaques and tumors | Yes | N/K | NA |
| **18** | M/68 | Specific cutaneous manifestation of ML | Maculopapular eruption | Yes | N/K | NA |
| **19** | M/53 | Sebaceous hyperplasia | Plaques | Yes | N/K | NA |
| **20** | F/67 | Lymphoid infiltrate | Plaques and tumors | No | N/K | NA |

| Case No. | Gender/ Age | Provided Clinical Diagnosis | Clinical Findings | History of ML | Interval, Month | Follow-Up (Months) |
|---|---|---|---|---|---|---|
| **21** | F/51 | Myelosarcoma | Solitary tumor | Yes | 24 | A+(2) |
| **22** | F/54 | Sweet syndrome | Edematous plaques | No | N/K | NA |
| **23** | F/70 | N/K | Solitary tumor | Yes | 9 | D+(23) |
| **24** | F/49 | N/K | Multiple tumors | No | 13 | D+(3) |
| **25** | F/59 | N/K | Multiple tumors | Yes | 13 | D+(5) |
| **26** | F/35 | N/K | Multiple tumors | Yes | 12 | D+(3) |
| **27** | F/21 | N/K | Multiple tumors | Yes | 6 | D+(12) |
| **28** | M/49 | Drug reaction vs viral eruption | Maculopapular eruption | No | 0 | D+(12) |
| **29** | M/29 | Drug reaction vs viral eruption | Maculopapular eruption | No | 0 | D+(1) |
| **30** | F/53 | Drug reaction vs viral eruption | Maculopapular eruption | No | 0 | D+(5) |
| **31*** | M/49 | N/K | Maculopapular eruption, infiltration of orbit | No | 2 | D+(1) |
| **32** | F/52 | N/K | Solitary tumor, swollen gums, infiltration of pharynx | Yes | 10 | D+(21) |
| **33** | F/70 | N/K | Plaques and tumors, swollen gums | No | 0 | D+(5) |
| **34** | F/27 | N/K | Maculopapular eruption, swollen gums | No | 0 | D+(15) |
| **35** | F/63 | Reaction by Tuberculin-test | Solitary tumor, swollen gums | No | 3 | D+(6) |
| **36** | F/83 | N/K | Plaques and tumors, infiltration of orbit | No | 0 | D+(12) |
| **37** | M/53 | Drug reaction vs viral eruption | Maculopapular eruption | No | 0 | D+(1) |
| **38** | F/70 | N/K | Maculopapular eruption | No | 0 | D+(1) |
| **39** | M/63 | N/K | Plaques and tumors, swollen gums | Yes | 11 | D+(4) |
| **40** | F/22 | N/K | Plaques and tumors | Yes | N/K | NA |
| **41** | M/79 | N/K | Plaques and tumors | Yes | N/K | D+(3) |
| **42** | F/45 | N/K | Plaques and tumors, infiltration of orbit | Yes | N/K | NA |
| **43** | M/63 | N/K | Plaques and tumors | Yes | 72 | D+(1) |
| **44** | M/63 | N/K | Plaques and tumors | Yes | 60 | D+(17) |
| **45** | M/67 | N/K | Plaques and tumors | Yes | N/K | NA |
| **46** | M/55 | Drug reaction vs viral eruption | Maculopapular eruption | Yes | 40 | D+(15) |
| **47** | M/85 | N/K | Solitary tumor | Yes | N/K | NA |
| **48** | M/67 | Drug reaction vs viral eruption | Maculopapular eruption | Yes | 36 | D+(13) |

A+, alive with systemic disease; D+, dead of leukemia; F, female; Interval, interval between skin biopsy and diagnosis of extracutaneous leukemia; M, male; ML, myelogenous leukemia; N/K unknown, NA, not available.

Two main, different patterns of skin infiltration were observed. One was characterized by larger, more infiltrated plaques and tumors that rose the clinical suspicion of specific skin manifestations of a known leukemia (*Figure 1* and *Figure 2, patient 39*) (22 cases).

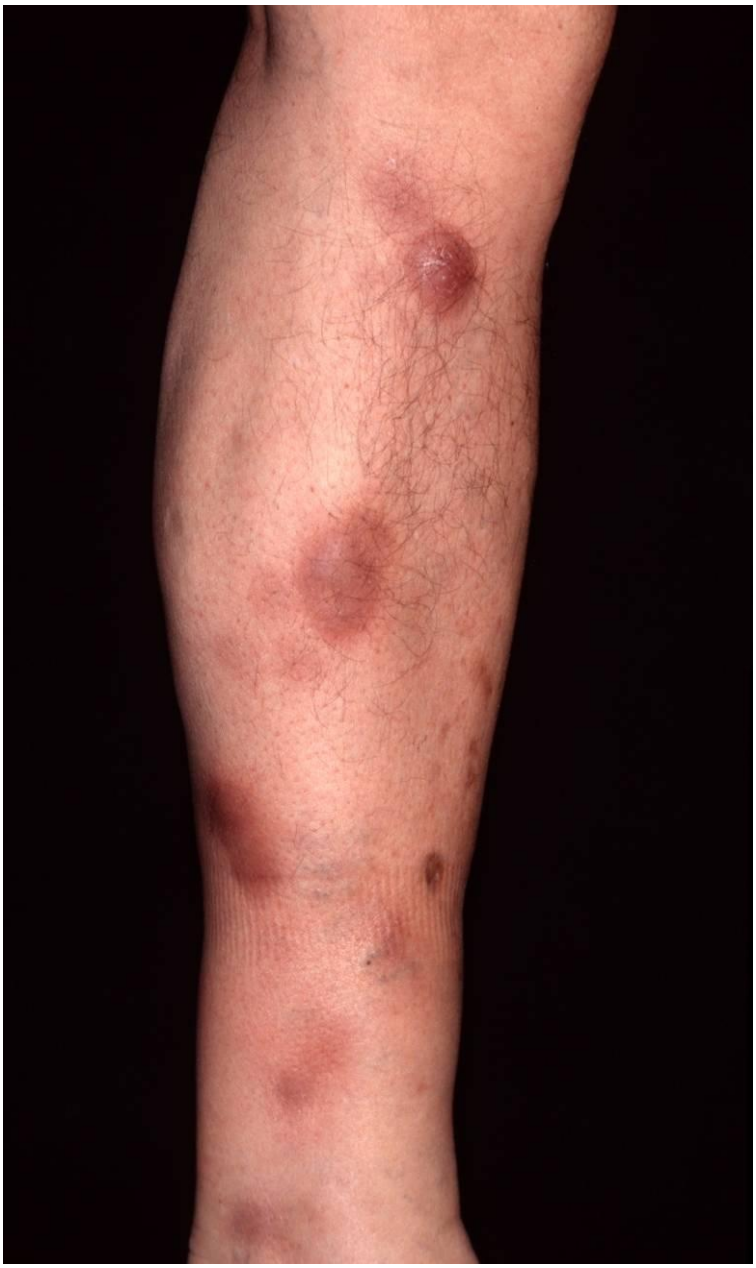

*Figure 1: Patient 39: Several red-brown plaques and tumors on the leg*

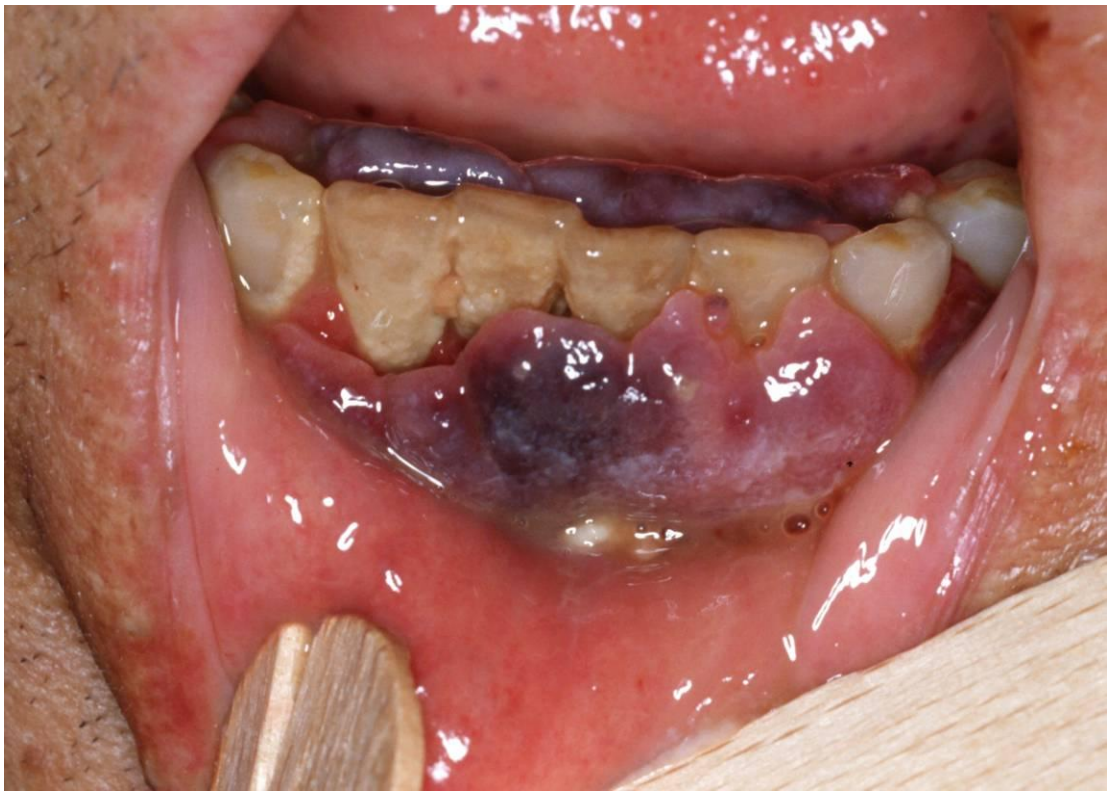

*Figure 2: Patient 39. Livid swollen gums is a typical manifestation of ML*

The second pattern was characterized by incospicuous, exanthematic macules and papules, sometimes with hemorrhagic aspect (26 cases) (*Figure 3*, patient 2 and *Figure 4*, patient 16). The most common clinical diagnosis was drug reaction. A history of ML was present in 9 of these patients. In 6 cases only (all of them with history of ML) a clinical differential diagnosis of cutaneous manifestations of ML was provided.

Finally, in 2 cases a clinical suggested diagnosis of Sweet's syndrome was made.

Follow-up data are summarized in *Table 1*. All patients developed systemic signs of ML within 0-72 months after skin biopsy. Twenty-eight patients died of leukemia (range: 1-32 months); 11 are alive with leukemia (range: 1-25 months). In 9 patients follow-up data were not available.

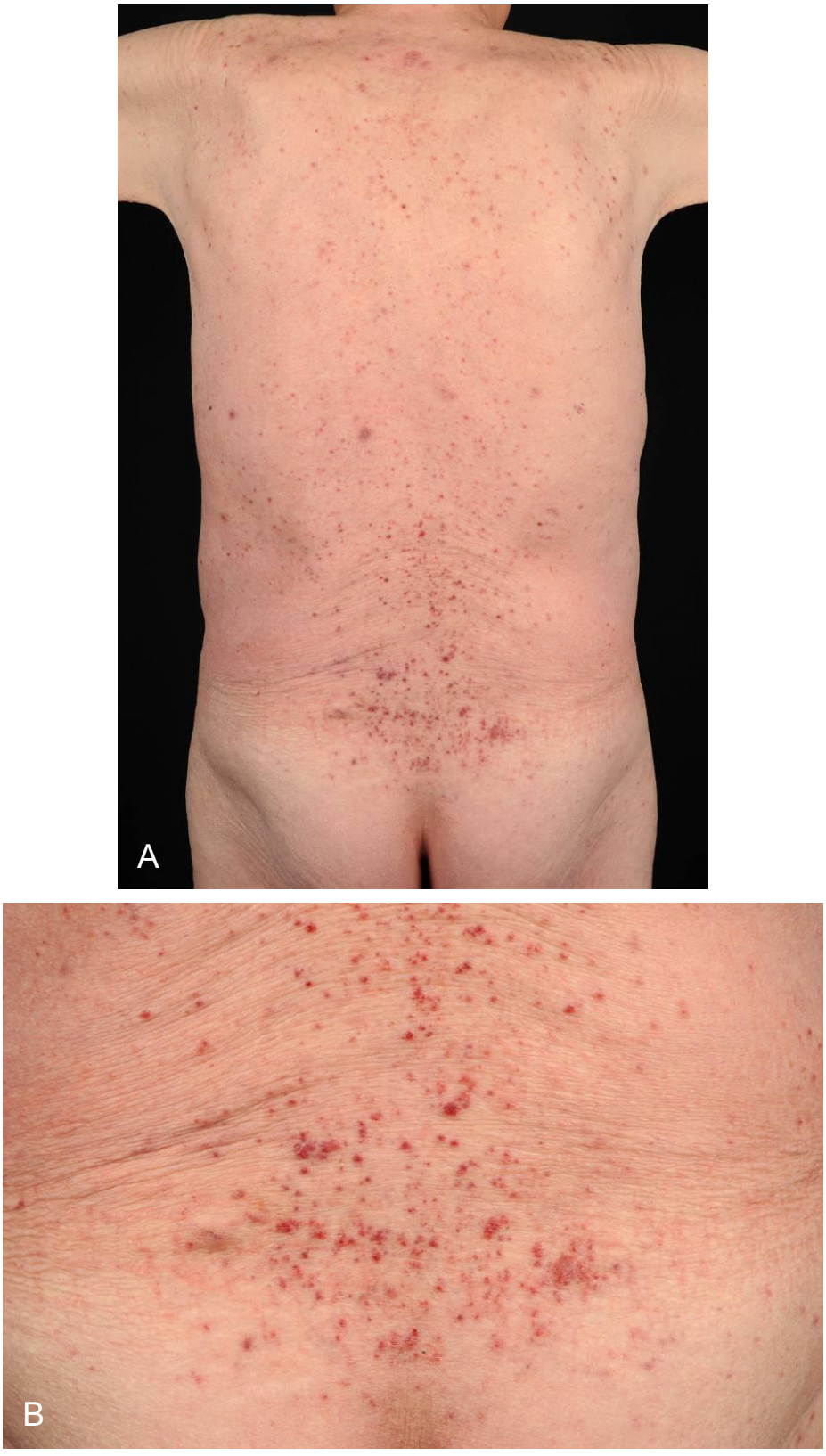


*Figure 3: Patient 2: (A) generalized hemorrhagic papules; (B) detail of clinical lesions. The provided clinical diagnosis was hemorrhagic drug eruption.*

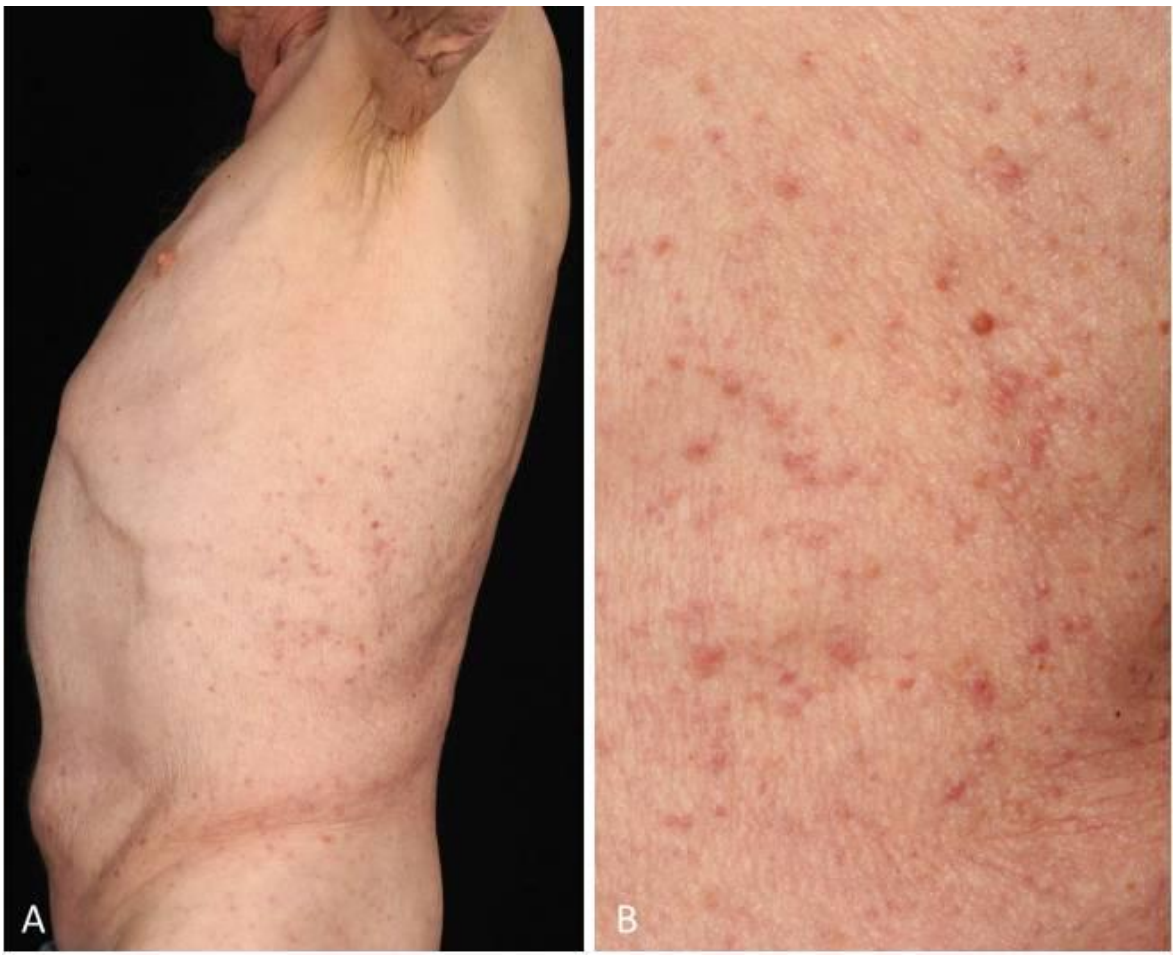


*Figure 4: Patient 16: (A) Generalized inconspicuous erythematous papules; (B) detail of the lesions. In this case the provided clinical diagnosis was drug eruption.*

## 3.2 Histopathological features

Different biopsies from the same patients gave similar results.

From a histopathological standpoint, too, two main patterns of cutaneous infiltrates of ML were observed.

The first pattern showed histopathologically dense, diffuse or nodular dermal infiltrates with perivascular and periadnexial accentuation and sparing of the upper papillary dermis (*Figure 5*, patient 36 and *Figure 6 A,* patient 24). Involvement of the subcutaneous tissue was observed. In most cases the infiltrate was composed of medium-sized, round to oval cells with a slightly eosinophilic cytoplasm and distinct, sometimes bilobular or kidney-shaped basophilic nuclei (atypical

monocytoid cells). In the majority of cases prominent single files of neoplastic cells between collagen were observed (*Figure 6* B, patient 24).

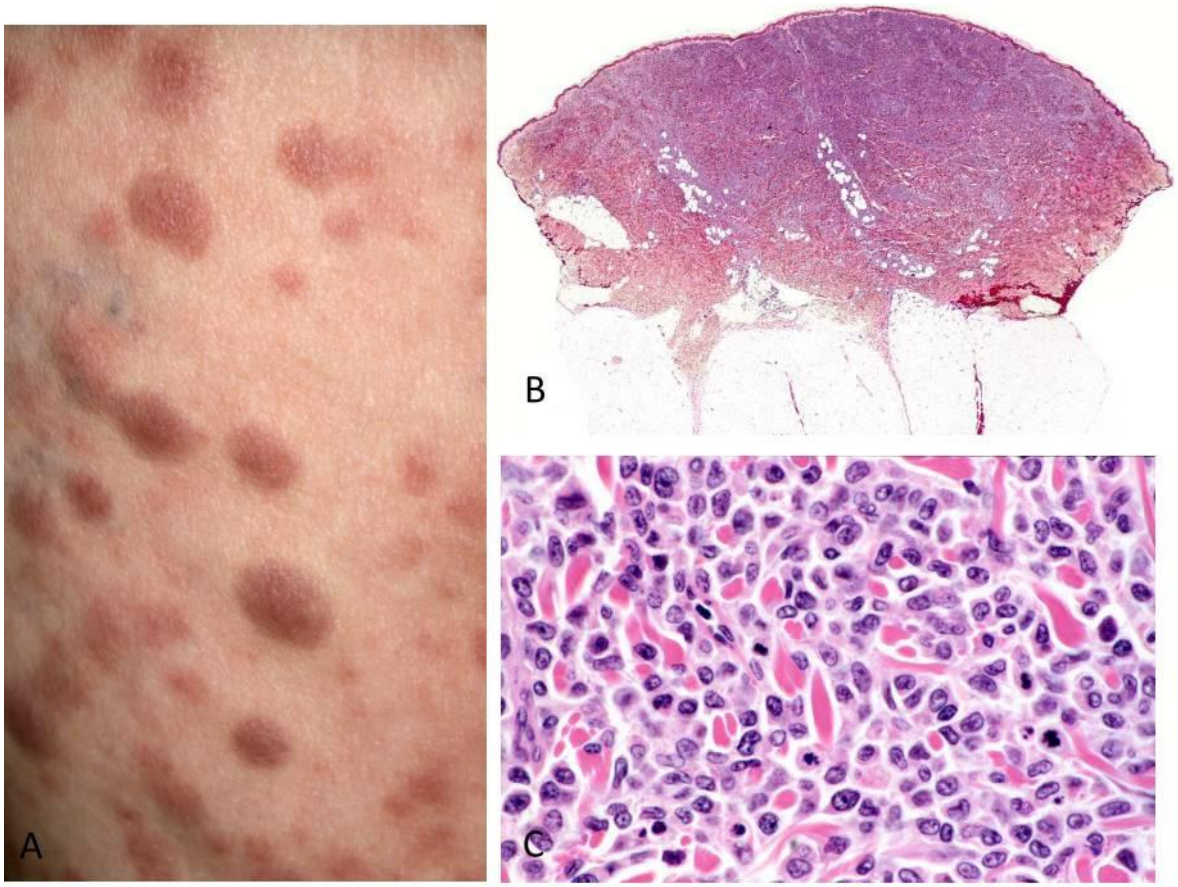


*Figure 5: Patient 36 (A) Several plaques and flat red-brown tumors on the thigh; (B) Nodular-diffuse infiltrate within the entire dermis; (C) Atypical myelomonocytic cells with several mitoses*

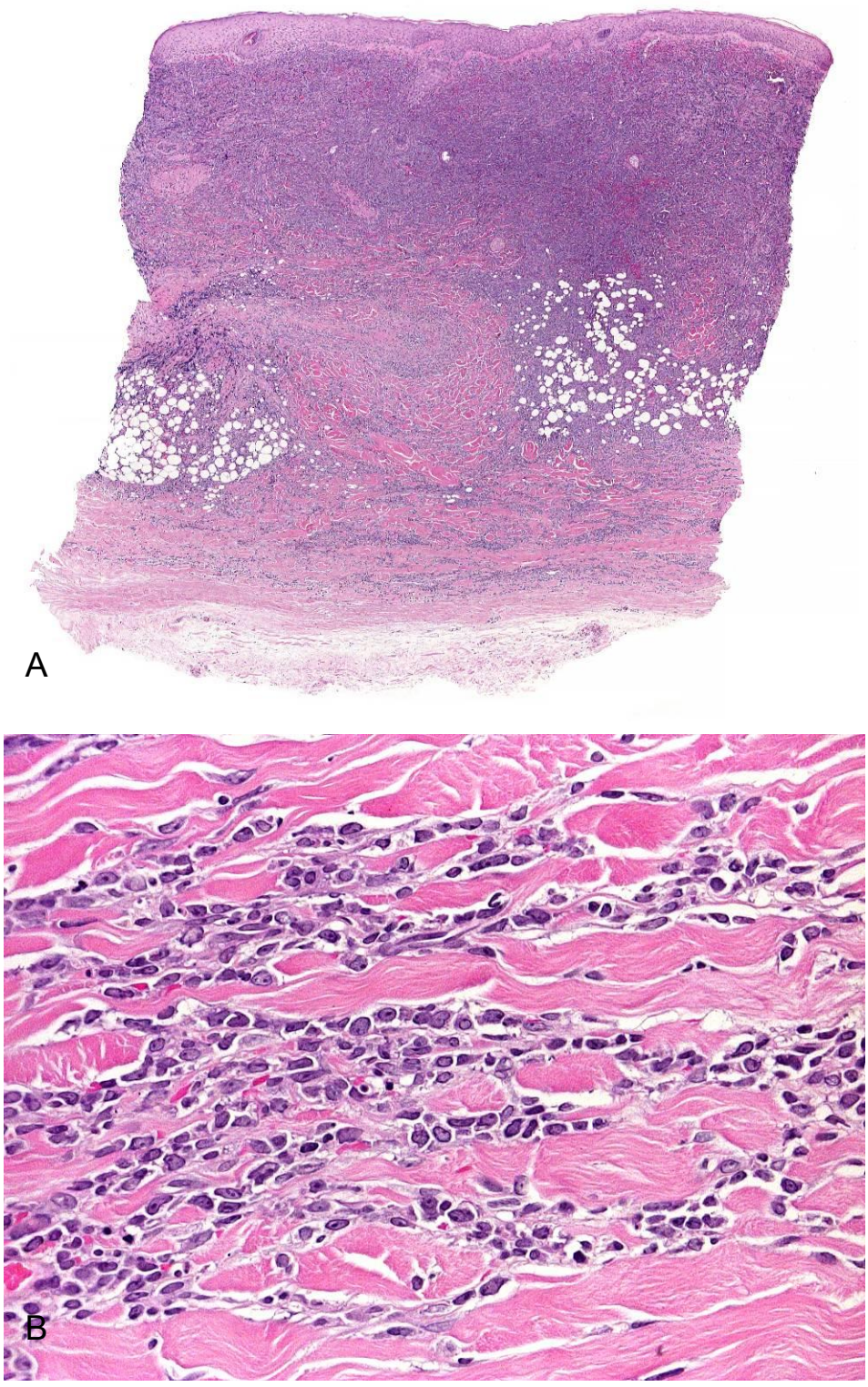


*Figure 6: Patient 24: (A) Diffuse infiltrate within the entire dermis and visible subcutaneous fat. (B) Linear arrangement of neoplastic cells ("Indian filing)*

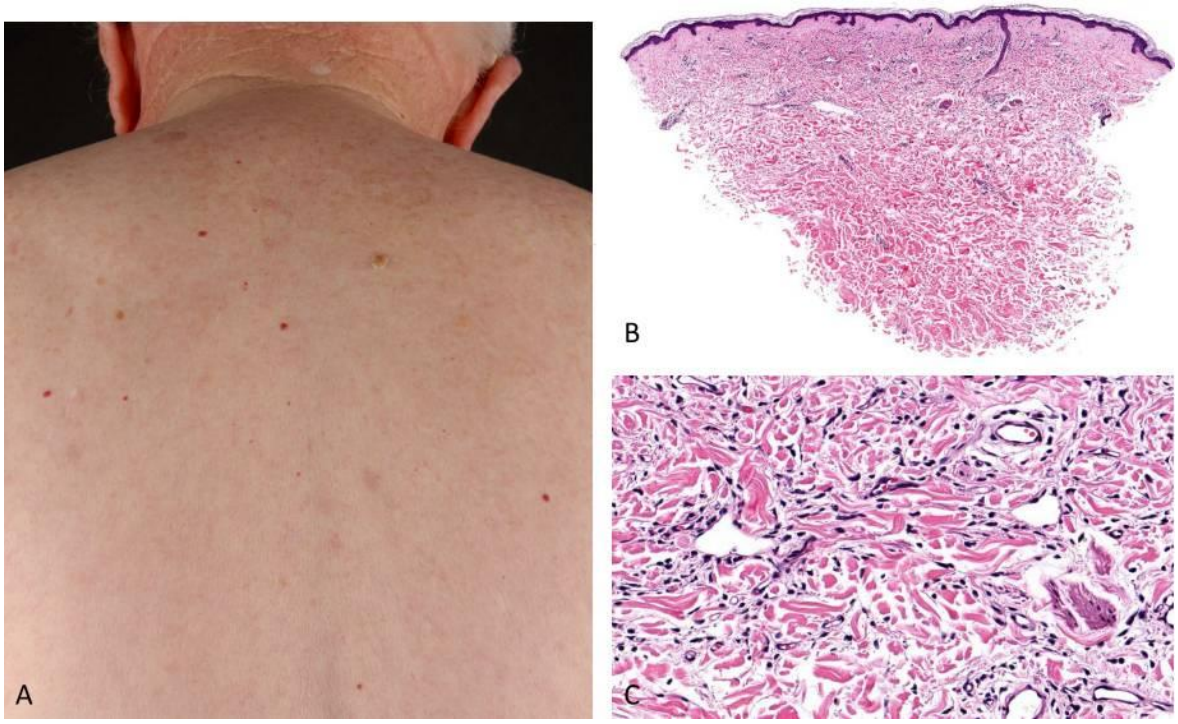


*Figure 7: Patient 12: (A) Clinical picture showing poorly demarcated inconspicuous macules and a few papules; (B) histology showing sparse dermal perivascular and interstitial infiltrates; (C) interstitial infiltrate with minimal "Indian filing" of cells between collagen bundles.*

The second pattern was characterized by sparse, superficial and mid-dermal infiltrates with minimal perivascular and periadnexal accentuation (*Figure 8* A, B patient 1 and *Figure 9* A, B, patient 16) and with only occasional single-array of cells between collagen bundles (Figure 7 A-C, patient 12). The epidermis and the subcutaneous tissues were not involved. The cytomorphology consisted mainly of medium-sized blastoid monocytoid cells with a characteristic eosinophilic cytoplasm and round-oval, slightly lobulated nuclei with finely dispersed chromatin. In some cases, the cells displayed small but distinct nucleoli. Variable amounts of inflammatory cells were present in most cases, but never represented the prominent cell population.

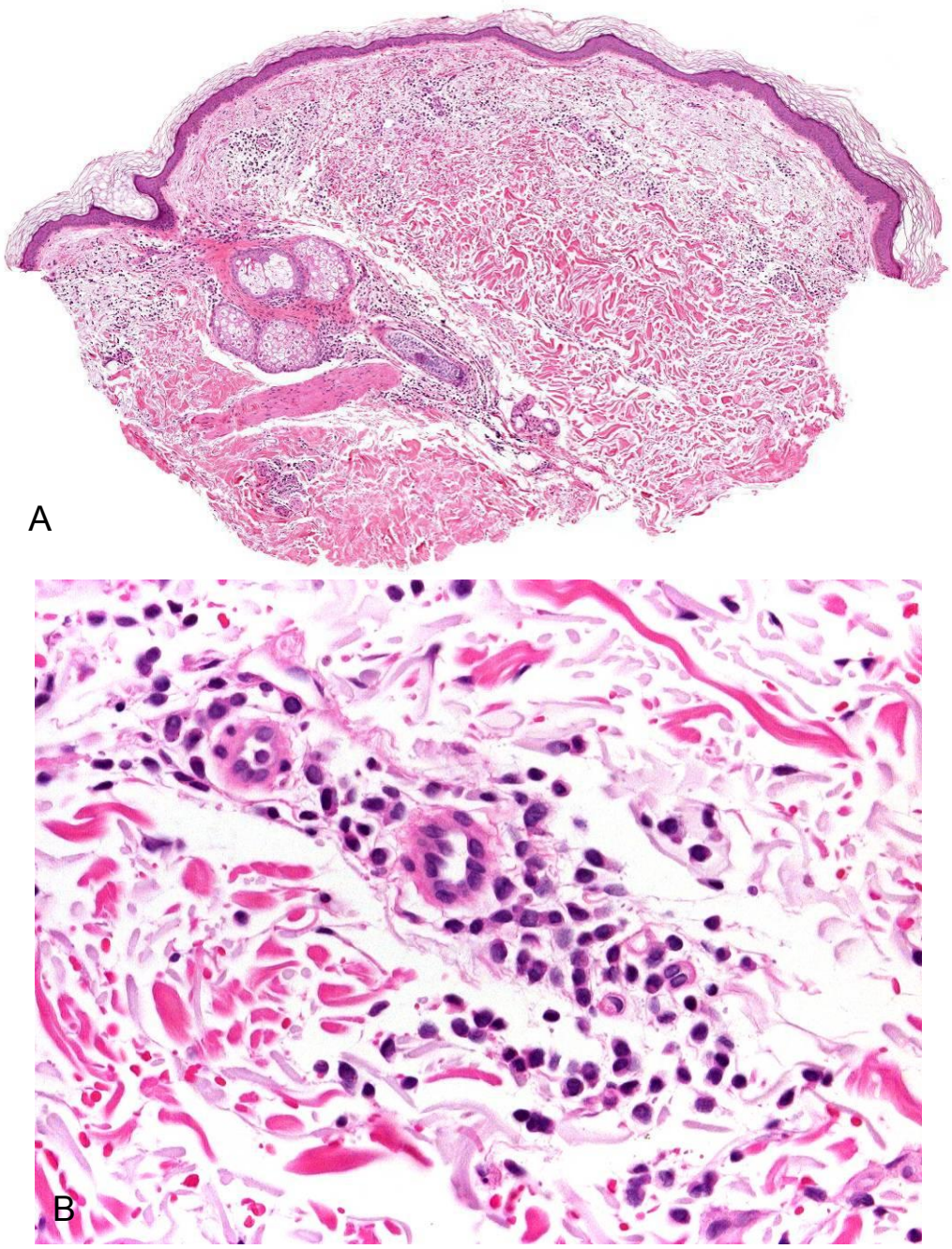


*Figure 8: Patient 1: (A) Sparse, superficial and mid-dermal infiltrates of mononuclear cells; (B) detail of perivascular monocytoid cells.*

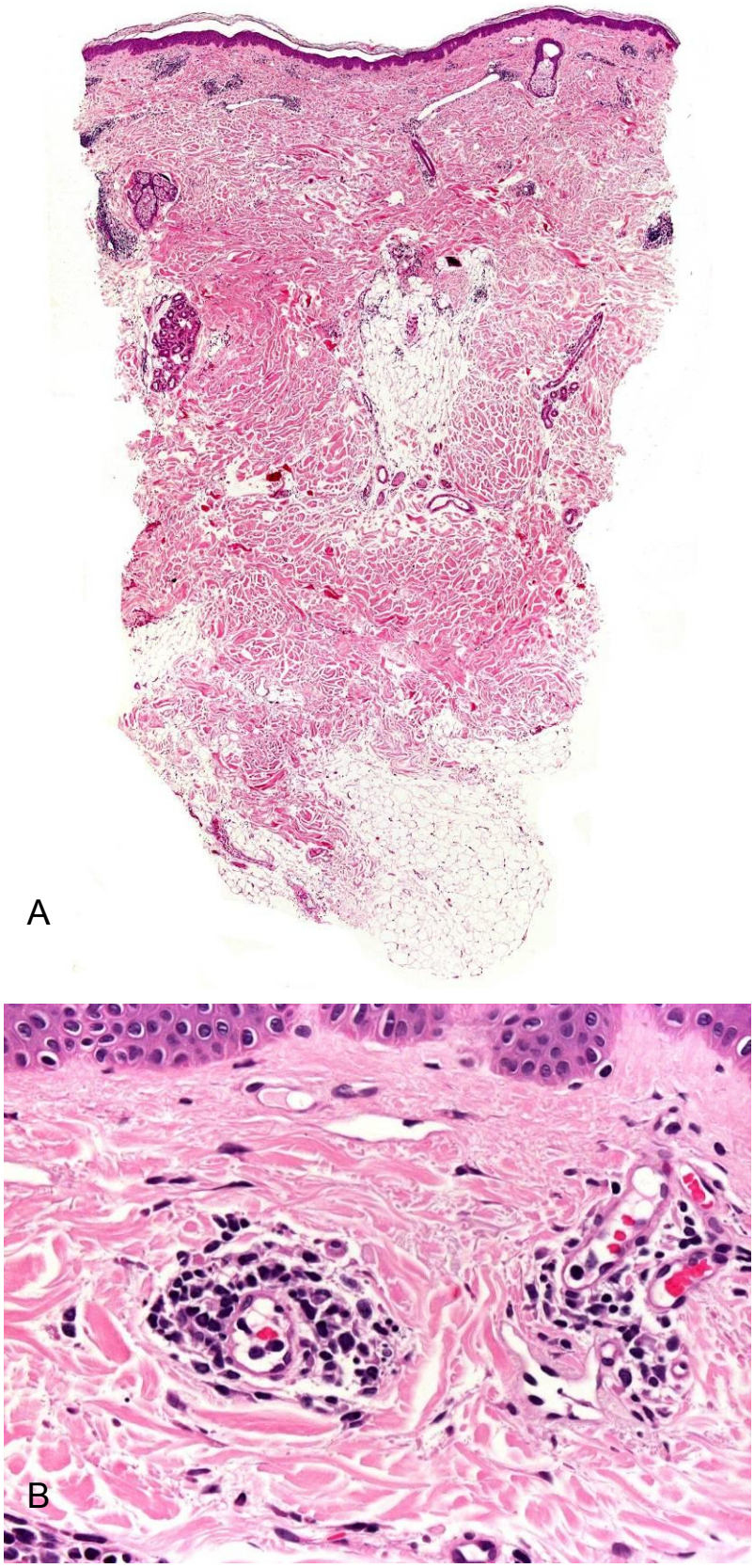


*Figure 9: Patient 16: (A) Superficial and mid-dermal sparse perivascular infiltrates; (B) perivascular cells with monocytoid appearance*

## 3.3 Histochemical and Immunohistochemical Findings

Neoplastic cells in the majority of cases were positive for the three markers CD4 in 47 cases (97.9%), (*Figure 10*, patient 25), CD68 in 45 cases (93.8%) (*Figure 11*, patient 16), MPO in 38 cases (79.2%), (*Figure 12,* patient 13 and *Figure 13*, patient 24) and NaSDCl in 30 cases (62.5 %). All cases were positive for CD43 *(Figure 14,* patient 25). Other markers were positive only in a minority of cases: CD33 in 18 cases (37.5%), CD56 in 10 cases (20.8%), CD34 in 5 cases (10.4%), CD117 in 4 cases (8.3%), CD123 in 4 cases (8.3%) and CD13 in 3 cases (6.3%). CD1a was negative in all cases. Stainings for T-cell and B-cell markers revealed positivity only a few reactive lymphocytes.

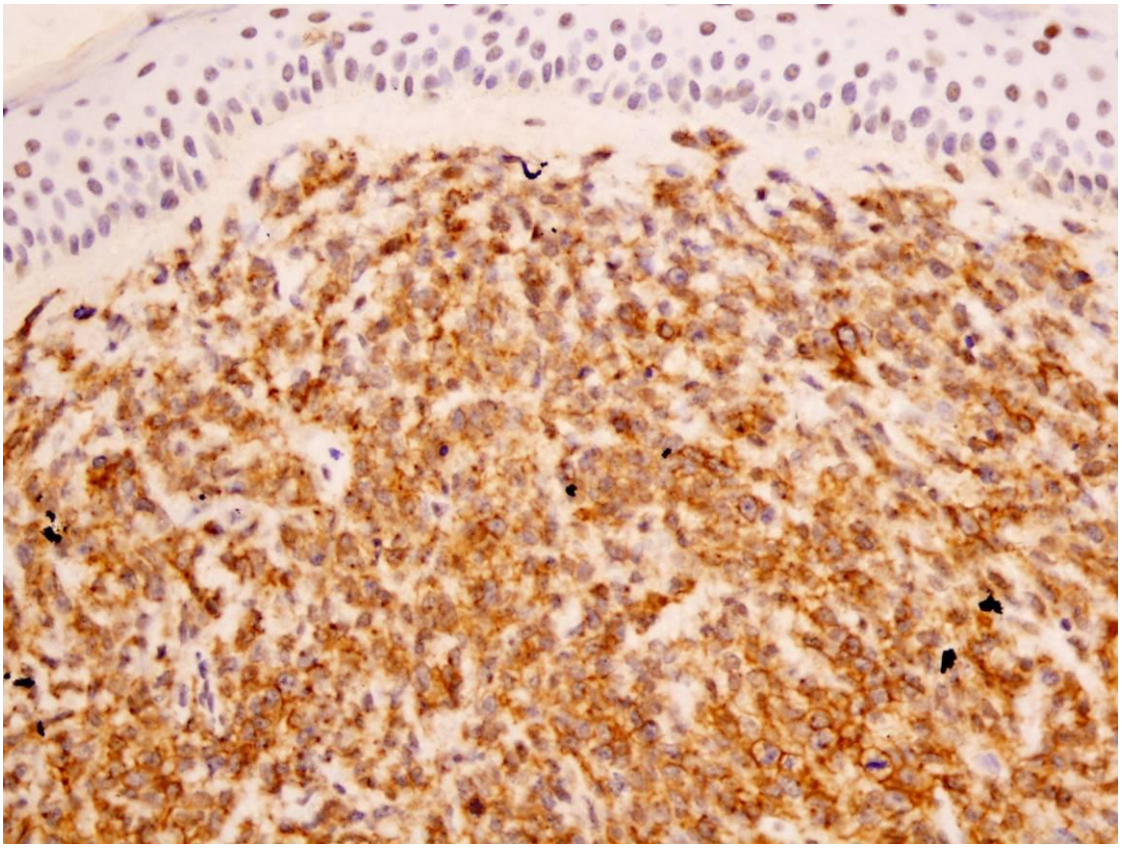

*Figure 10: Patient 25: Staining for CD4 positive in neoplastic cells*

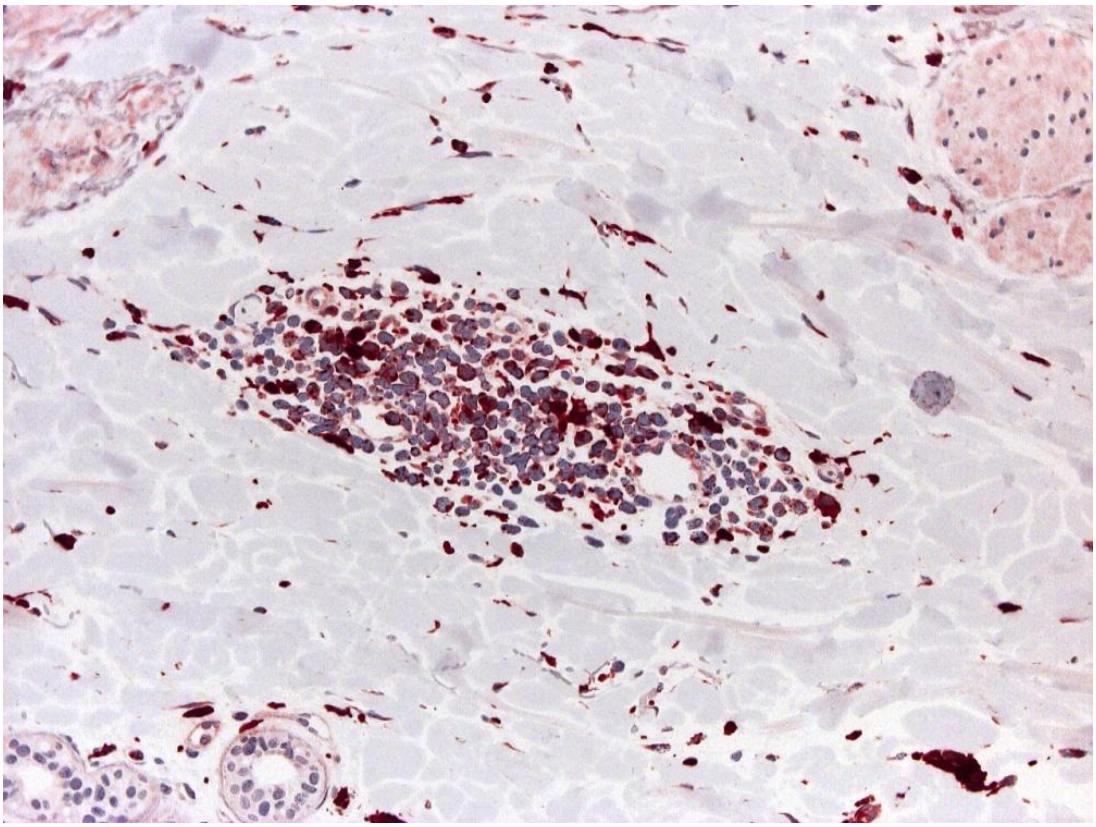

*Figure 11: Patient 16: Staining for CD68 revealed positivity of most neoplastic cells*

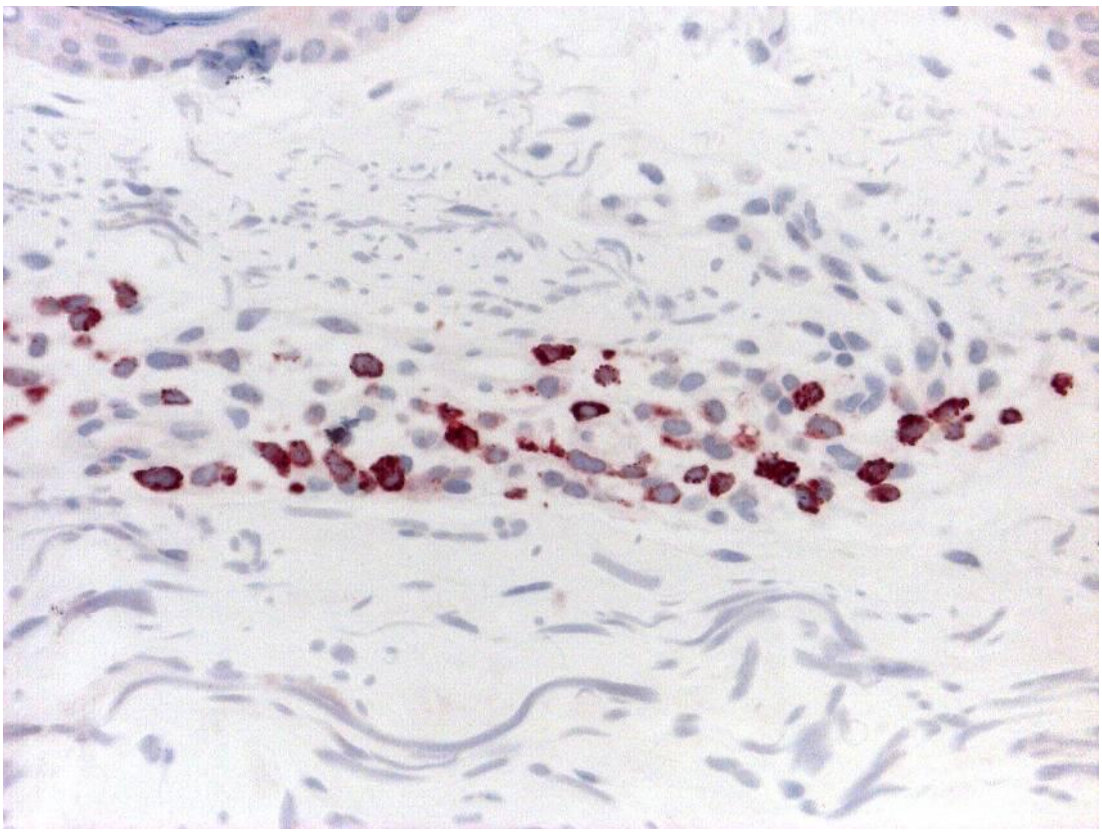

*Figure 12: Patient 13: Neoplastic cells positive for MPO*

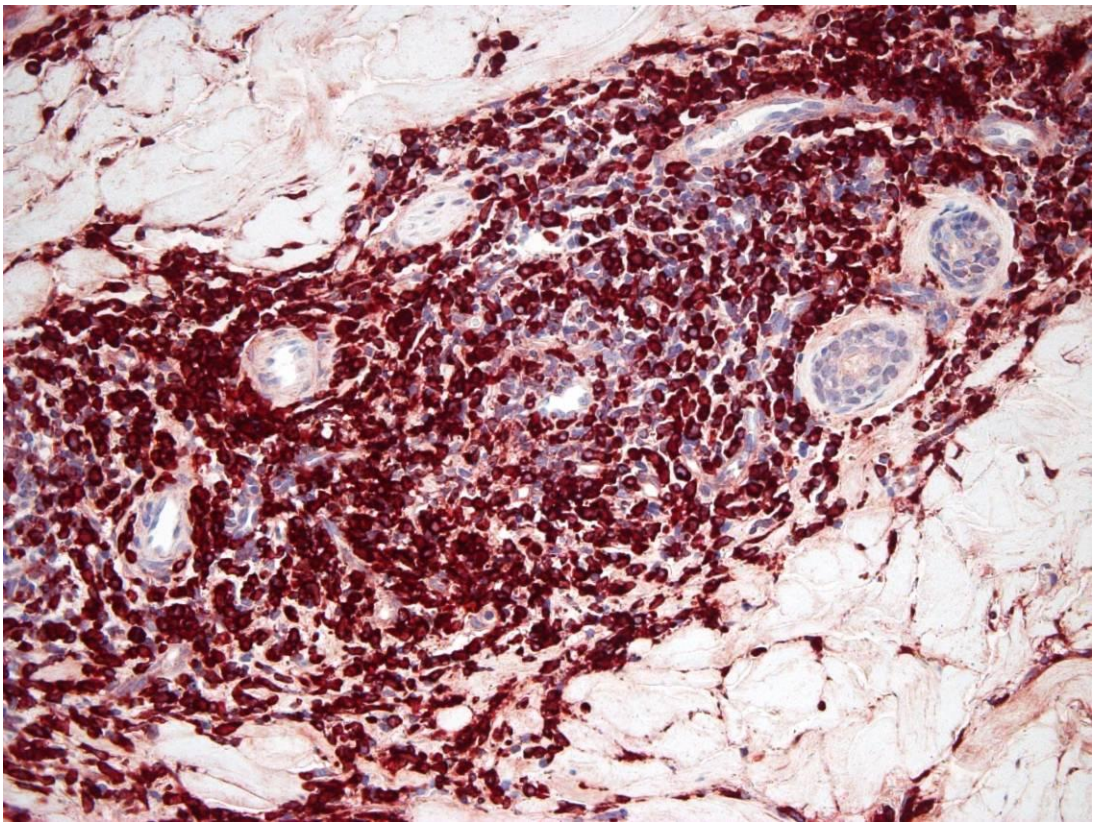

*Figure 13: Patient 24: Strong positivity for MPO deceted in all neoplastic cells*

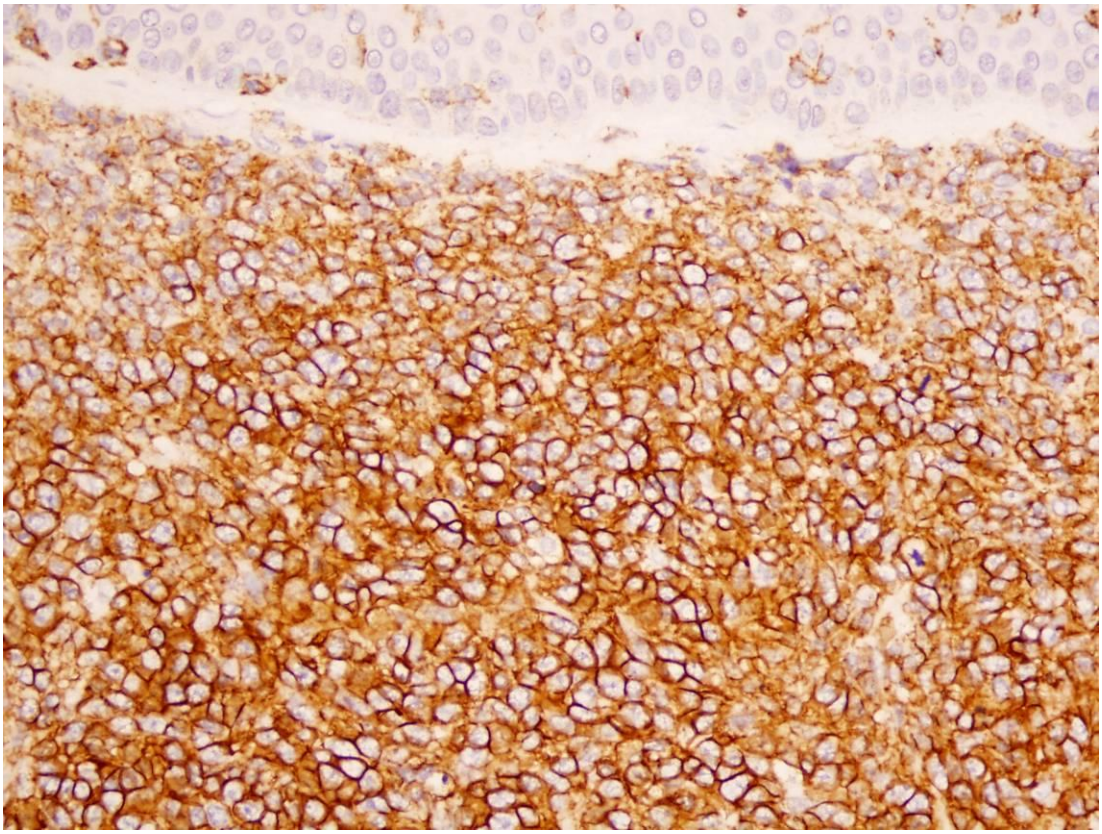

*Figure 14: Patient 25: Neoplastic cells positive for CD43*

# 4 Discussion

We presented 48 patients with cutaneous infiltrates as specific manifestations of ML (both CML and AML). Provisional clinical diagnoses included drug eruption, viral exanthema, Sweet syndrome, leukocytoclastic vasculitis, granuloma facial and psoriasis among others.

From the histopathological standpoint, two main patterns of skin infiltration by ML could be observed: one was characterized by dense, diffuse or nodular dermal infiltrates with perivascular and periadnexial accentuation and sparing of the upper papillary dermis. In a majority of cases prominent single files of neoplastic cells ("Indian filing") between collagen were observed. The second pattern showed sparse, superficial and mid-dermal infiltrates with minimal perivascular and periadnexal accentuation, with only occasional single-array of cells between collagen bundles. The epidermis and the subcutaneous tissues were not involved. Variable amounts of inflammatory cells were present in most cases, but never represented the prominent cell population.

Cases presenting histopathologically with the second pattern may represent a pitfall in the histopathological diagnosis, as they may be misinterpreted as an inflammatory skin disorder. In fact, many of these cases clinically were not suspected to be related to ML and a history of ML was present only in 25 patients and in only 6 cases, a specific manifestation of ML was mentioned as a differential diagnosis.

Although clinicopathologic features of specific cutaneous manifestations of ML usually allow a precise diagnosis, as in 27 of our cases, clinical manifestations mimicking benign skin conditions have been described [Chang 2003, Benez 2001, Hsaio 2011, O´Donnell 1982, Kim 2010]. Accurate diagnosis therefore relies on a high index of suspicion together with the ability to recognize the cytomorphologic features of tumor cells [Berger 1973, Benet 2011]. In this context, unlike conventional dermatoses, specific infiltrates of ML, even when sparse, are characterized by a predominance of myelomonocytic cells with only small numbers of lymphocytes.

Immunohistochemistry is crucial in order to correctly classify these cases. Previous studies have shown that CD68, lysozyme, and CD33 have very good sensitivity, being positive in approximately 90% of cutaneous ML cases [Cibull 2008, Benet 2011]. The markers MPO, CD4, and CD163 were positive in 50% – 70% of cases; CD117, CD56 and CD14 in 30%– 40% of cases; and CD34, CD56, CD123, and CD303 in less than 20% of cases [Cibull 2008, Benet 2011, Harms 2010]. These findings are comparable to those observed in our study, where phenotypic analysis reveled similar features irrespective of the histopathological pattern.

In our study, the markers CD68 and MPO showed a positivity in 93.8% and 79.2% of cases, respectively. In addition, we could demonstrate that staining for NaSDCl is also a sensitive marker, being positive in 62.5% of cases. A lower percentage of MPO-positive cases (42%) was found by Cronin and colleagues [Cronin 2009]. CD68 is a marker of monocytic/histiocytic lineage, and it is not surprising for ML to be consistently immunoreactive to it. [Jeffery 2011]. CD68 is considered as the most sensitive immunohistochemical marker for the detection of myeloid leukemia cutis regardless of FAB subtype [Cibull 2008]. In fact, absence of CD68 staining in cutaneous manifestations of ML is rare and should prompt to consider also alternative diagnoses. Positivity for CD68 is useful in differentiating ML from drug reactions, as only a minority of cells (20%) is positive for CD68 in skin specimens of this last condition. [Yawalkar 2000].

In the study by Cronin et al, [Cronin 2009] CD56 was positive in 47% of cases of cutaneous ML, which is higher than the percentage observed in our study (20.8%). The reasons for these discrepant results may reside in the selection and classification of cases. In fact, positivity for CD56 in cases of cutaneous ML should be differentiated from other CD56 positive hematologic neoplasms, particularly BPDCN [Cota 2010]. Because CD4 is usually positive both in ML and BPDCN, and because CD68 can be expressed by neoplastic cells of BPDCN (although with a granular pattern different from that observed in cutaneous ML, see below), differentiation of these two entities relies on a wide panel of antibodies including myelomonocytic markers, TCL-1, BDCA-2, and CD123.

Immunohistochemical studies in cutaneous ML are of particular importance in those cases presenting with scant infiltrates of neoplastic cells, as reactive, inflammatory dermatoses represents an important differential diagnosis. Thus, a broad panel of antibodies should be applied any time that cutaneous manifestations of ML represent a differential diagnostic concern.

Besides mimicking reactive, benign skin conditions, cutaneous ML infiltrates may also arise within pre-existing inflammatory or neoplastic skin conditions, posing further diagnostic problems. One of our patients (case 8, previously reported by Metzler et al [Metzler 1997] had a history of psoriasis and developed ML with specific manifestations of the disease within the psoriatic plaques. Histopathological examination showed large atypical mononuclear cells in the upper dermis along with typical findings of psoriasis. The cells were positive for MPO, NaSDCl, CD68, CD74, CD43, and lysozyme. Similarly, Diaz-Cascajo and Bloedern-Schlicht [Diaz-Cascajo 1998] reported a case of a basal cell carcinoma in association with a dense myeloblastic infiltrate in a patient with chronic ML. It was postulated that circulating blast cells were attracted to neoplastic or inflammatory lesions in response to antigenic stimuli.

In this context, one of the most important differential diagnoses of cutaneous specific manifestations of ML is with Sweet syndrome. One study revealed CD68 and MPO positivity in 6 of 11 cases of conventional Sweet syndrome with co-expression of the 2 markers in all cases [Corazza 2008]. Intense immunoreactivity was especially seen in the histiocytoid variant of Sweet syndrome.[Requena 2005]. It was postulated that immature myeloid cells were released by the BM in early acute stages of the disease in this condition, thus accounting for the peculiar histologic and phenotypic features. On the other hand, the presence of specific cells of ML has been described within lesions of Sweet syndrome [Urano 1999], thus complicating the diagnosis in such cases. However, conventional Sweet syndrome presents histopathologically with dense superficial and mid-dermal neutrophilic infiltrates accompanied by moderate to intense papillary dermal edema, in contrast with the minimal inflammatory infiltrate seen in the patients with ML described in this study.

Cutaneous ML must be differentiated from BPDCN. In this context, it must be underlined that a relationship between these 2 entities has been postulated [Facchetti 2008, Kazakov 2003]. In fact, similarities in clinical presentation, histology and immunophenotype have been described [Bekkenk 2004]. In addition, evolution into ML can be observed in 20% of cases of BPDCN, and sometimes an association with a previous myelodisplastic syndrome has been recorded as well [Assaf 2007].

BPDCN is phenotypically characterized by coexpression of CD4 and CD56, the expression of CD123 and TCL-1, and the absence of any specific myeloid, T-lymphoid, B-lymphoid, or NK-lymphoid lineage markers [Julia 2014]. In addition, double negativity for CD56 and CD123 has not been observed in cases of BPDCN [Cota 2010, Julia 2014]. However, cases of BPDCN lacking expression of CD4, CD56 and/ or CD123, TCL-1 have been reported in the literature [Ascani 2008, Cota 2010, Mariafioti 2008].

Julia reported in a study that when only CD4, CD56, and CD123 are positive and BDCA-2 and TCL-1 are negative the differential diagnosis should be carefully considered because CD56 and CD123 are also frequently expressed in cutaneous ML. In such cases, it is important to demonstrate myeloid marker negativity [Julia 2014]. However, lesions of specific cutaneous manifestations of ML tend to be negative for CD56 and CD123. As noted before, the positivity of only one of both markers CD56 and CD123 is not sufficient to differentiate BPDCN from ML. In this case markers which show higher sensitivity for ML compared to BPDCN should be tested [Mariafioti 2008].

Our study revealed that most cases of cutaneous ML are positive for CD4, MPO, CD68, and NaSDCl. Of these 4 markers, CD4 cannot be used in the differential diagnosis with BPDCN, as it is expressed in most cases of this hematological disorder as well. On the other hand, positivity for MPO and/or NaSDCl rules out the diagnosis of BPDCN [Cota 2010, Cerroni 2014]. A wide panel of antibodies should be always applied, particularly in cases of ML that do not express CD68 and/or MPO [Cronin 2012].

Besides quantitative differences between ML and BPDCN, the pattern of CD68 positivity, too, is different among these two entities: cutaneous ML shows a diffuse cytoplasmatic positivity of most neoplastic cells, whereas BPDCN is characterized by a granular positivity of a minority of neoplastic cells [Cota 2010, Cerroni 2014]. Petrella and Facchetti have reported CD68 is positive in about of 50% of BPDCN cases and they also described granular positivity in the neoplastic cells [Petrella 2005, Facchetti 2008]. Gao and colleagues consider the expression of CD68 usually negative in BPDCN, and postulated that positivity for CD68 could indicate a transformation into ML [Gao 2015].

In contrast to cutaneous ML, where inflammatory dermatitis-like infiltrates could be observed in 56% of cases, a similar deceptive presentation was found only in 20% of BPDCN biopsies [Cota 2010]. In these cases neoplastic cells were admixed with reactive lymphocytes, sometimes resembling the picture of a cutaneous inflammatory disorder [Cota 2010].

As already mentioned, cutaneous ML presenting with sparse infiltrates should also be differentiated from inflammatory skin conditions. An important differential diagnosis is represented by the pseudolymphomatous variant of GA, because the histiocytic cells may be positive for CD68 with a pattern similar to that observed in cutaneous ML. The pseudolymphomatous type of GA may have some histological resemblance to ML as it is characterized by perivascular infiltrates and an indian filing-like arrangement of histiocytes. However, in the pseudolymphomatous variant of GA most of the infiltrate is represented by lymphocytes, unlikely what is seen in cutaneous ML, and the phenotype is positive only for CD68 and CD163 but never for other myelogenous markers [Cota 2012].

In summary, we presented a group of patients with cutaneous infiltrates as specific manifestations of ML, often representing a problem in the histopathological diagnosis and differential diagnosis from other hematological conditions or from inflammatory dermatoses. Accurate morphologic and phenotypic correlation together with a high index of suspicion allows a precise diagnosis and classification of these cases.

# 5 Bibliography


1. Argyrakos T, Rontogianni D, Karmiris T, et al. Blastic natural killer (NK)-cell lymphoma: report of an unusual CD4 negative case and review of the CD4 negative neoplasms with blastic features in the literature. Leukem Lymph. 2004;45:2127–2133.

2. Ascani S, Massone C, Ferrara G, et al. CD4-negative variant of CD4+/CD56+ hematodermic neoplasm: description of three cases. J Cutan Pathol. 2008;35:911–915.

3. Assaf C, Gellrich S, Whittaker S, et al. CD56-positive haematolo- gical neoplasms of the skin: a multicentre study of the Cutaneous Lymphoma Project Group of the European Organisation for Research and Treatment of Cancer. J Clin Pathol. 2007;60:981–989.

4. Baksh FIC Nathan D, Richardson VV, Kestenbaum T, Woodroof .1. Leukemia cutis with prominent giant cell reaction. *Am .1 Dermatopathol* 1998:20:48-52.

5. Benet C, Gomez A, Aguilar C *et al.* Histologic and Immunohistologic Characterization of Skin Localization of Myeloid Disorders A Study of 173 Cases. Am J Clin Pathol. 2011;135:278-90.

6. Benez A, Metzger S, Metzler G, Fierlbeck G. Aleukemic leukemia cutis presenting as benign-appearing exanthema. *Acta Derm Venereol.* 2001;81:45-7.

7. Berger BJ, Gross PR, Daniels RB, Lankton BB. Leukemia cutis masquerading as guttate psoriasis. Arch Dermatol. 1973;108:416-8.

8. Bekkenk MW, Jansen PM, Meijer CJLM, et al. $CD56^{+}$ hemato- logical neoplasms presenting in the skin a retrospective analysis of 23 new cases and 130 cases from the literature. Ann Oncol. 2004;15:1097–1108.

9. Cerroni L, Smolle J, Soyer HP, Martinez Aparicio A, Kerl H. Immunophenotyping of cutaneous lymphoid infiltrates in frozen and paraffin-embedded tissue sections: a comparative study. J Am Acad Dermatol. 1990;22:405-13.

10. Cerroni L, Skin Lymphoma. The Illustrated Guide. 4th ed. Oxford: Wiley-Blackwell; 2014:296–319.

11. Cibull TL, Thomas AB, O'Malley DP, Billings SD. Myeloid leukemia cutis: a histologic and immunohistochemical review. *J Cut Pathol.* 2008;35:180-5.

12. Chang HY, Wong KM, Bosenberg M, McKee PH, Haynes HA. Myelogenous leukemia cutis resembling stasis dermatitis. *J Am Acad Dermatol*. 2003;49:128-9

13. Corazza M, Lauriola MM, Borghi A, Marzola A, Virgili A. Sweet's syndrome: a retrospective clinical, histopathological and immunohistochemical analysis of 11 cases. Acta Derm Venereol. 2008;88:601-6.

14. Cota C, Vale E, Viana I, Requena L, Ferrara G, Anemona L, Metze D, Fink-Puches R, Wiesner T, Cerroni L. Cutaneous manifestations of blastic plasmacytoid dendritic cell neoplasm – Morphologic and phenotypic variability in a series of 33 patients. Am J Surg Pathol. 2010;34:75-87.

15. Cota C, Ferrara G, Cerroni L. Granuloma annulare with prominent lymphoid infiltrates (“pseudolymphomatous”granuloma annulare). Am J Dermatopathol. 2012 May;34(3):259-62.

16. Cronin DMP, George TI, Reichard K, Sundram UN. Immunophenotypic analysis of myeloperoxidase-negative leukemia cutis and blastic plasmacytoid dendritic cell neoplasm. Am J Clin Pathol. 2012 Mar;137(3):367-76.

17. Cronin DMP, George TI, Sundram UN. An Updated Approach to the Diagnosis of Myeloid Leukemia Cutis. Am J Clin Pathol. 2009;132:101-10.

18. Deguchi M, Tsunoda T, Yuda F, Tagami H. Sweet´s syndrome in acute myelogenous leukemia showing dermal infiltation of leukemic cells. Dermatology 1997;194:182-184.

19. Desch JK, Smoller BR. The spectrum of cutaneous disease in leukemias. J Cut Pathol. 1993;20:407-10.

20. Diaz-Cascajo C, Bloedern-Schlicht N. Cutaneous infiltrates of myelogenous leukemia in association with pre-existing skin diseases. J Cutan Pathol. 1998;25:185-6.

21. Facchetti F, Jones D, Petrella T. Blastic plasmacytoid dendritic cell neoplasm. In: Swerdlow SH, Campo E, Hazzis NL, et al, eds. WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues. Lyon: IARC press; 2008:145–147.

22. Feuillard J, Jacob MC, Valensi F, et al. Clinical and biologic features of CD4+ CD56+ malignancies. Blood. 2002;99:1556–1563.

23. Gao NA, Wang XX, Sun JR, Yu WZ, Guo NJ. Blastic plasmacytoid dendritic cell neoplasm with leukemic manifestation and ETV6 gene rearrangement: A case report. Exp Ther Med. 2015 Apr;9(4):1109-1112.

24. Garcia C, Gardner D, Reichard K. CD163: A Specific Immunohistochemical Marker for Acute Myeloid Leukemia With Monocytic Differentiation Appl Immunohistochem Mol Morphol 2008;16:417–421.

25. Harms PW, Bandarchi B, Ma L. CD163 expression in leukemia cutis. J Cutan Pathol. 2010;37:953-7.

26. Hejmadi RK, Thompson D, Shah F, Naresh KN. Cutaneous presentation of aleukemic monoblastic leukemia cutis - a case report and review of literature with focus on immunohistochemistry. *J Cut Pathol.* 2008;35:46-9.

27. Hsiao PF, Lin J, Wu YH. Therapy-related leukemia cutis with histopathologic changes resembling xanthogranuloma. J Am Acad Dermatol. 2011;65:460-2.

28. Herling M, Teitell MA, Shen RR, et al. TCL1 expression in plasmacytoid dendrtitic cells (DC2) and the related CD4 CD56 blastic tumors of skin. Blood 2003,101:5007-5009.

29. Jeffery M., Shashikant K., Friederike H., et al. Immunohistochemical Analysis of Monocytic Leukemias. Am J Clin Pathol. 2011;135:720-730.

30. Jegalian A, Buxbaum N, Facchetti F, et al. Blastic plasmacytoid dendritic cell neoplasm in children: diagnostic features and clinical implications. Hematologica 20010; 95(11):1873-89.

31. Julia F, Petrella T, Beylot-Barry M, Bagot M, Lipsker D, et al. Blastic plasmacytoid dendritic cell neoplasm: clinical features in 90 patients. Br J Dermatol. 2013 Sep;169(3):579-86.

32. Julia F, Dalle S, Duru G, Balme B, Vergier B, Ortonne N, et al. Blastic plasmacytoid dendritic cell neoplasms: clinico-immunohistochemical correlations in a series of 91 patients. Am J Surg Pathol. 2014 May;38(5):673-80.

33. Kaddu S, Zenahlik P, Beham-Schmid C, Kerl H, Cerroni L. Specific cutaneous infiltrates in patients with myelogenous leukemia: a clinicopathologic study of 26 patients with assessment of diagnostic criteria. *J Am Acad Dermatol.* 1999;40:966-78.

34. Kaiserling E, Horny HP, Geerts ML, Schmid U. Skin involvement in myelogenous leukemia: morphologic and immunophenotypic heterogeneity of skin infiltrates. *Mod Pathol*. 1994;7:771-9.

35. Kazakov DV, Mentzel T, Burg G, et al. Blastic natural killer-cell lymphoma of the skin associated with myelodysplastic syndrome or myelogenous leukemia: a coincidence or more? Br J Dermatol. 2003;149:869–876.

36. Kim HS, Choi MJ, Kim HO, Park YM. Leukemia cutis limited to the needle puncture sites. J Dermatol. 2010;37:393-5.

37. Kuwabara H, Nagai M, Yamoaka G, et al. Specific skin manifestations in CD56 positive acute myeloid leukemia. J Cutan Pathol 1999;26:1-5.

38. Martínez Escanamé M., Zuriel D., Tee Shang-I., Fried I., Massone C. Cerroni L., Cutaneeous Infiltrates of Acute Myelogenous Leukemia Simulating Inflammatrory Dermatoses, Am J Dermatopathol 2013; 35: 419-424.

39. Marafioti T, Paterson JC, Ballabio E, et al. Novel markers of normal and neoplastic human plasmacytoid dendritic cells. Blood. 2008;111:3778–3792.

40. Massone C, Chott A, Metze D, et al. Subcutaneous, blastic natural killer (NK), NK/T-cell, and other cytotoxic lymphomas of the skin. A morphologic, immunophenotypic, and molecular study of 50 patients. Am J Surg Pathol. 2004;28:719–735.

41. Metzler G, Cerroni L, Schmidt H, Soyer HP, Sill H, Kerl H. Leukemic cells within skin lesions of psoriasis in a patient with acute myelogenous leukemia. J Cutan Pathol. 1997;24:445-8.

42. Petrella T, Bagot M, Willemze R, et al. Blastic NK-cell Lymphomas (agranular $CD4^+CD56^+$ hematodermic neoplasms). A review. Am J Clin Pathol. 2005;123:662–675.

43. Requena L, Kutzner H, Palmedo G, et al. Histiocytoid Sweet syndrome: a dermal infiltration of immature neutrophilic granulocytes. Arch Dermatol. 2005;141:834-842.

44. Sepp N, Radaskiewicz T, Meiger CJ, Smolle J, Seewan H, Fritsch P, Kerl H. Specific skin manifestations in acute leukemia with monocytic differentiation. A morphologic and immunohistochemical study of 11 cases. Cancer 1993; 71: 124.

45. Swerdlow S.H, Campo, E., Harris, N.L, et al.,eds. WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues. Lyion:IARC Press, 2008:109-144.

46. Tomasini C, Quaglino P. Novelli M. Fierro MT. "Aleukemic" granulomatous leukemia cutis. *Am J Dermatopathol* 1998:20: 417-421.

47. Urano Y, Miyaoka Y, Kosaka M, Kabe K, Uchida N, Arase S. Sweet's syndrome associated with chronic myelogenous leukemia: demonstration of leukemic cells within a skin lesion. J Am Acad Dermatol. 1999;40:275-9.

48. Yawalkar N, Egli F, Hari Y, Nievergelt H, Braathen LR, Pichler WJ. Infiltration of cytotoxic T cells in drug-induced cutaneous eruptions. Clin Exp Allergy 2000;30:847-55.