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Management of primary cutaneous lymphomas during the COVID-19 pandemic

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Abstract Primary cutaneous lymphomas are defined as a heterogenic group of T- and B-cell non-Hodgkin lymphomas that present initially in the skin. Patients with primary cutaneous lymphomas are at a higher risk for developing complications in case of infection with the novel coronavirus severe acute respiratory syndrome coronavirus 2.
The coronavirus disease 2019 (COVID-19) pandemic has affected the established diagnostic approach, staging, and therapeutic guidelines in patients with primary cutaneous lymphomas. In the light of the current global health crisis, management of primary cutaneous lymphomas needs to be adjusted. The key to achieving this is to balance the optimal control of the lymphoma, with a minimal increase of the personal risk for COVID-19 exposure and complications.
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Background

Primary cutaneous lymphomas (PCLs) are defined as a heterogenic group of T- and B-cell non-Hodgkin lymphomas that present in the skin without extracutaneous involvement at the time of diagnosis.[1] They are the second most common form of extranodal lymphoma. The group of PCLs exhibits distinct clinical, histologic, immunophenotypic, and genetic characteristics.[2]

The coronavirus disease 2019 (COVID-19) outbreak that originated in December 2019 in Wuhan, China, is caused by a novel betacoronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[3] The pandemic has been accelerating since the beginning of 2020 and is challenging the health care systems worldwide with hundreds of thousands infected daily.[4]

Evidence shows that although most patients with COVID-19 could be classified as mild or moderate, around 14% of cases are reported to be severe, and 5% critical,[5] with a mortality rate of around 1%.[6,7] Several risk factors for severe disease course and complications have been identified, including age older than 65, innate immune deficiencies or acquired immunosuppression (malignancies, uncontrolled HIV/AIDS) or iatrogenic immunosuppression by drugs (long-term corticosteroid intake, chemotherapy, bone marrow or organ transplantation).[8]

Based on our current knowledge of the COVID-19 pandemic, patients who suffer from PCLs may represent a risk group for potential life-threatening complications in case of infection with SARS-CoV-2. This is due to the immunosuppression related to the malignancy itself, in association with the potential use of immunosuppressive agents to control the lymphoma.[9,10] The advanced age, potential comorbidities (eg, diabetes, hypertension),[9,11,12] and risk of exposure to SARS-CoV-2 during in-office visits may represent independent risk factors for lymphoma patients.

In the light of the current global health crisis, the management of PCLs, including its diagnosis, staging, and therapy, requires adjustment. The key represents the balance

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of optimal disease control with a minimal increase of the personal risk for COVID-19 exposure and complications in the case of infection.

The COVID-19 pandemic affects the classification (in terms of risk stratification for complication of COVID-19), diagnostic approach, staging, and therapeutic choice in patients with PCLs.

Classification of PCLs and identification of low- and high-risk types during the COVID-19 pandemic

PCLs represent a heterogenic group of malignancies, which include cutaneous T-cell lymphomas (CTCLs) and cutaneous B-cell lymphomas (CBCLs). According to the current data, in the Western world, 75-80% of all PCLs are CTCLs and 20-25% are CBCLs.[1] The PCLs are classified according to the World Health Organization–European Organization for Research and Treatment of Cancer (WHO-EORTC) consensus classification from 2005,[13] with its update from 2018.[14]

Recently the United States Cutaneous Lymphoma Consortium published recommendations for treatment of cutaneous lymphomas during the COVID-19 pandemic.[15] This publication identifies low-risk, intermediate-low risk, intermediate-high risk, and high-risk categories of PCLs, as influenced by the potential complications of infection with SARS-CoV-2. The level of risk for each type of cutaneous lymphoma, is presented in Table 1.

According to the available data, **low-risk** patients, who do not receive systemic treatment, are as susceptible to infections as the general population. This group includes mycosis fungoides (MF) stages IA, IB with limited skin involvement or with patches only, Pagetoid reticulosis, lymphomatoid papulosis, some rare types of CTCLs (eg, primary cutaneous $CD4^+$ small/medium T-cell lymphoproliferative disorder, primary cutaneous acral $CD8^+$ T-cell lymphoma). Some CBCLs, including primary cutaneous marginal zone lymphoma and primary cutaneous follicular center lymphoma, are also classified as low-risk for complications in case of COVID-19 infection.

Patients with late-stage or aggressive PCLs are at **high risk** of a complicated COVID-19 clinical course due to at least two factors: older age and immunosuppression. The latter could result either from the malignancy itself or from the treatment (iatrogenic immunosuppression). Common findings associated with immunosuppression in patients with PCLs are **lymphopenia** and a decreased number of functioning CD4 cells that may potentially be associated with the expansion of the malignant $CD4^+$ clone.[16] Lymphopenia is a poor prognostic factor in confirmed infection with SARS-Cov-2 virus[17]; thus the preexisting lymphopenia could predispose to a worse disease course in COVID-19 patients with underlying PCLs.[16]

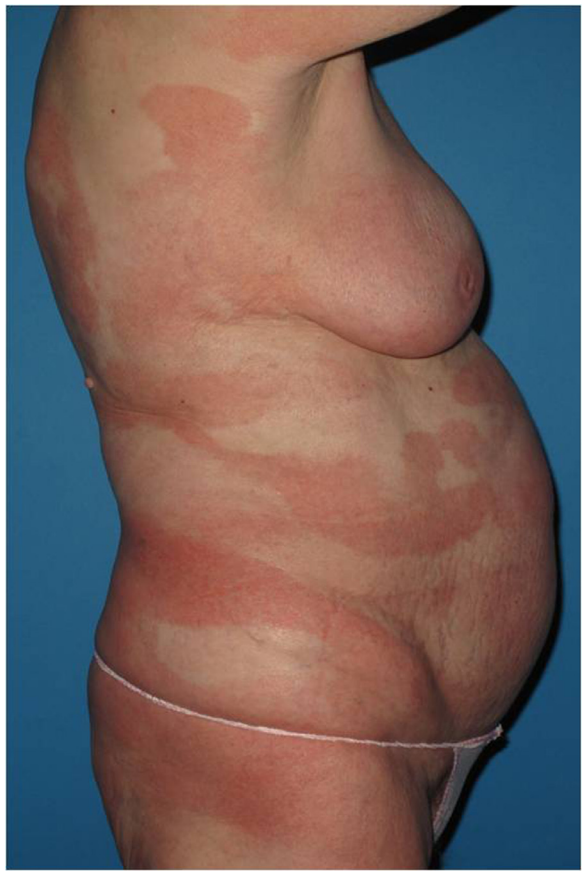

Figure 1 Early patch/plaque mycosis fungoides, stage IB.

Management of cutaneous T-cell lymphomas

Diagnostic approach to CTCLs during COVID-19

According to the Short-Term Recommendations for the Management of T-Cell and Primary Cutaneous Lymphomas during COVID-19,[18] determining the initial diagnosis remains of high importance.

Although there are no current real-life data on how the COVID-19 pandemic affects the diagnostics of CTCLs, the diagnosis of CTCLs may be delayed due to several factors. For example, the diagnosis may be postponed due to the fear of patients becoming infected while visiting the hospital or even self-isolation of older people at home. In some circumstances the whole diagnostic algorithm has been complicated due to transformation of some dermatologic units into COVID-19 treatment units and the admission only on emergency in the remaining functioning dermatology clinics.

Mycosis fungoides

MF is the most common type of PCL; it presents clinically with patches and plaques in early stages (IA-IIA) (Figure 1) and cutaneous tumors (Figure 2) and erythroderma (Figure 3)

Table 1 Relative frequency and risk for COVID-19 complications in patients with PCLs, classified according to the 2018 update of the WHO-EORTC classification and the United States Cutaneous Lymphoma Consortium's recommendations.[1,15]

WHO-EORTC Classification 2018	Frequency, %	5-year DSS, %	Relative risk of COVID-19 complications
Cutaneous T-cell lymphomas			
MF*	39	88	**Low** (stages IA, IB—limited BSA, or patch only) **Intermediate-low** (stages IB—extensive patches, plaques, IIA) **Intermediate-high** (stages IIB, III) **High** (stage IV, or transformed MF)
MF variants			
Folliculotropic MF	5	75	**Intermediate-low**
Pagetoid reticulosis	<1	100	**Low**
Granulomatous slack skin	<1	100	**Intermediate-low**
SS	2	36	**High**
Adult T-cell leukemia/lymphoma	<1	NDA	**NDA**
Primary cutaneous CD30$^+$ LPDs			
C-ALCL	8	95	**Intermediate-low**
LyP	12	99	**Low**
Subcutaneous panniculitis-like T-cell lymphoma	1	97	
Extranodal NK/T-cell lymphoma, nasal type	<1	16	**High**
Chronic active EBV infection	<1	NDA	**NDA**
Primary cutaneous peripheral T-cell lymphoma, rare subtypes			
Primary cutaneous γ/δ T-cell lymphoma	<1	11	**High**
CD8$^+$ AECTCL (provisional)	<1	31	**High**
Primary cutaneous CD4$^+$ small/medium T-cell lymphoproliferative disorder (provisional)	6	100	**Low**
Primary cutaneous acral CD8$^+$ T-cell lymphoma (provisional)	<1	100	**Low**
Primary cutaneous peripheral T-cell lymphoma, NOS	2	15	**NDA**
Cutaneous B-cell lymphomas			
PCMZL	9	99	**Low**
PCFCL	12	95	**Low**
PCDLBLC, LT	4	56	**High**
EBV-positive mucocutaneous ulcer (provisional)	<1	100	**NDA**
Intravascular large B-cell lymphoma	<1	72	**NDA**

BSA, body surface area; C-ALCL, cutaneous anaplastic large-cell lymphoma; CBCL, cutaneous B-cell lymphoma; CD8$^+$ AECTCL, primary cutaneous acral CD8$^+$ T-cell lymphoma; CTCL, cutaneous T-cell lymphoma; DSS, disease-specific survival; EBV, Ebstein-Barr virus; LPD, lymphoproliferative disorder; EORTC, European Organisation for Research and Treatment of Cancer; LyP, lymphomatoid papulosis; MF, mycosis fungoides; NDA, no data available; NOS, not otherwise specified; PCDLBLC, LT, primary cutaneous large B-cell lymphoma, leg type; PCFCL, primary cutaneous follicular center lymphoma; PCMZL, primary cutaneous marginal zone lymphoma; SS, Sézary syndrome; WHO, World Health Organization.

in late stages (IIB-IVB). The definitive diagnosis of early MF remains a challenge because its clinical and histopathologic characteristics may be unspecific and indistinguishable from some inflammatory dermatoses. Additional studies may include assessment of aberrant T-cell antigen expression by immunohistochemical staining (eg, loss of CD2, CD5, CD7), and detection of clonal rearrangements T-cell receptor by polymerase chain reaction.[19]

In the era of COVID-19, some histopathologic laboratories have been temporarily closed, thus breaking the chain of diagnosing new cases of MF. Even in pre-COVID-19 times, the correct diagnosis in suspected early MF, where distinction from benign inflammatory dermatoses is difficult, may have been delayed up to 3 to 4 years from the initial manifestations.[20] With this expected delay in the initial diagnoses, we believe that an additional 2- to 3-month delay of the identification of the new early-stage MF cases would not significantly complicate the management of these cases, given the 88% 5-year disease-specific survival.[1] On the other hand, late-stage MF is often associated with an aggressive clinical course and poor prognosis and a 5-year overall survival between 10% and 20%.[21] The delay in diagnosis of these patients due to COVID-19 pandemic may decrease their chance for effective treatment due to rapid disease progression.

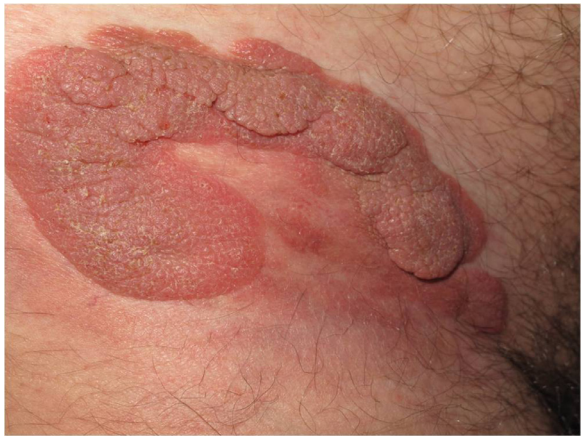

Figure 2 Advanced mycosis fungoides with cutaneous tumors, stage IIB.

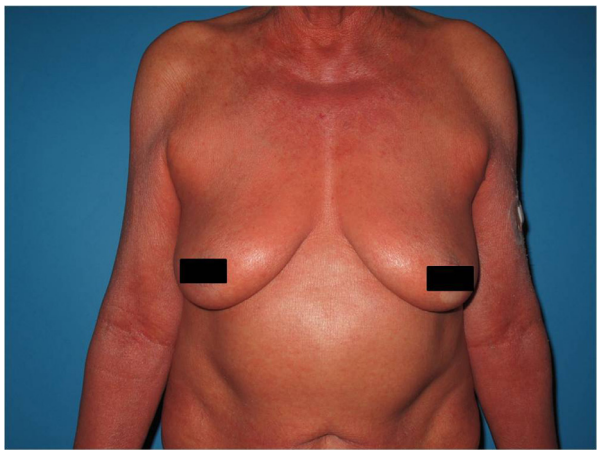

Figure 3 Erythrodermic mycosis fungoides, stage IIIB.

Sézary syndrome

Sézary syndrome (SS) is defined as a rare leukemic variant of CTCL; it presents with the triad: pruritic erythroderma (Figure 4), generalized lymphadenopathy, and clonal neoplastic T-cells (Sézary cells) in the skin, lymph nodes, and peripheral blood.

The diagnosis of SS includes histopathologic examination of lesional skin biopsy, although histologic features, such as epidermotropism, may be more discrete as in MF and often unspecific.[22] Demonstration of the involvement of the peripheral blood is crucial for the diagnosis of SS. The criteria for involvement include absolute Sézary cell count of 1000/mL, or an expanded $CD4^+$ T-cell population resulting in a CD4/CD8 ratio $\geq$10, $CD4^+/CD7^-$ cells $\geq$40%, or $CD4^+/CD26^-$ cells $\geq$30%.[1]

The timely diagnosis of the SS remains a high priority due to the 36% 5-year disease-specific survival[1] and the aggressive clinical course. For these reasons, treatment should not be delayed.

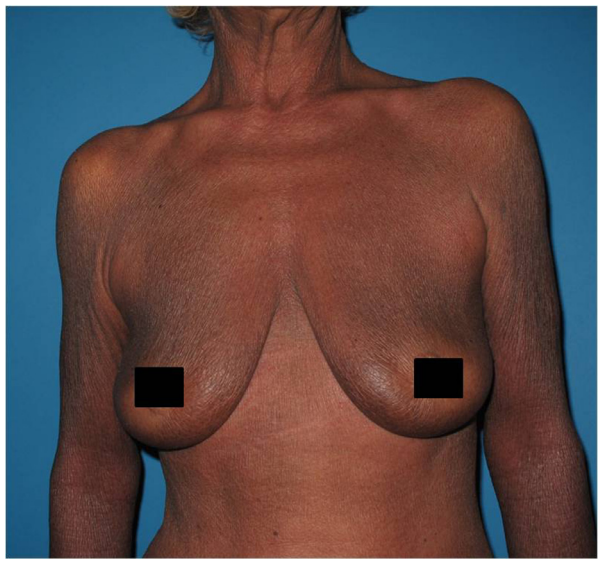

Figure 4 Melanoerythrodema in Sézary syndrome, stage IVA_1.

Two cases of infection with SARS-Cov-2 in patients with Sézary syndrome have been published.[23] The first patient was a 56-year-old woman with transformed SS who had been on gemcitabine therapy for 2 months at the time of infection with SARS-CoV-2. She had a normal chest-x ray examination but died due to progressive SS within 5 days. The second patient was a 78-year old woman with newly diagnosed Sézary syndrome. After 6 weeks of treatment with dexamethasone and interferon alfa with only a partial response, plus two subsequent cycles of gemcitabine, the patient developed a dry cough and respiratory distress. The computed tomography scan showed bilateral ground glass opacities affecting more than 50% of both lungs, and the nasopharyngeal swab was positive for SARS-Cov-2. The patient died of respiratory failure within 8 days of the onset of these findings.

CTCLs other than MF/SS

Non-MF/SS subtypes of CTCLs should be distinguished from MF/SS during the initial diagnosis. The course of the disease, the prognosis, and the treatment are highly variable between the various non-MF/SS lymphoma subsets.[13,24] The $CD30^+$ lymphoproliferative disorders—lymphomatoid papulosis (Figure 5) and cutaneous anaplastic large-cell lymphoma—represent the largest group of non-MF/SS PCLs.

Staging of CTCLs during COVID-19

Mycosis fungoides/ Sézary Syndrome

The major tool for risk stratification and a "risk-adapted" approach to treatment in MF/SS remains the ISCL (International Society for Cutaneous Lymphomas) and EORTC revised TNMB (tumor, node, metastasis, blood) staging[19,24] (Tables 2 and 3).

Table 2 Revised TNMB staging for MF/SS.[19,24]

T (Skin)	N (Nodes)
T1 Limited patch/plaque (<10% of total skin surface)	N0 No clinically abnormal LNs
T2 Generalized patch/plaque (≥10% of total skin surface)	N1 Clinically abnormal LNs, Dutch grade 1 or NCI LN O-2 (clone ±)
T3 Tumors	N2 Clinically abnormal LNs, Dutch grade 2 or NCI LN O-3 (clone ±)
T4 Generalized erythroderma	N3 Clinically abnormal LNs, Dutch grade 3-4 or NCI LN O-4 (clone ±)
	Nx Clinically abnormal LNs, no histologic examination
M (viscera)	**B (Blood)**
M0 No visceral involvement	B0 No significant blood involvement
M1 Visceral involvement	B1 Low blood tumor burden
	B2 High tumor burden*

LN, lymph node; MF, mycosis fungoides; NCI, National Cancer Institute; SS, Sézary syndrome.
* CD4/CD8 ratio ≥10, or $CD4^+CD7^-$ cells ≥40%, or $CD4^+CD26^-$ ≥30% of lymphocytes, or other aberrant expression of pan T-cell markers.

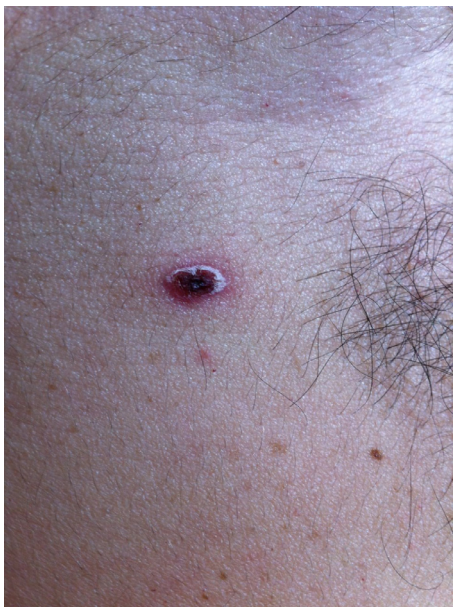

Figure 5 Lymphomatoid papulosis.

Table 3 Revised TNMB staging for MF/SS.[24]

Clinical Stages	TNMB Classification			
IA	T1	N0	M0	B0-1
IB	T2	N0	M0	B0-1
IIA	T1-2	N1-2	M0	B0-1
IIB	T3	N0-2	M0	B0-1
IIIA	T4	N0-2	M0	B0
IIIB	T4	N0-2	M0	B1
IVA_1	T1-4	N0-2	M0	B2
IVA_2	T1-4	N3	M0	B0-2
IVB	T1-4	N0-3	M1	B0-2

Staging workup in MF/SS is important for selecting the choice of appropriate treatment. Patients with limited patch/plaque (stage IA) disease have similar survival to the age-matched disease-free control population.[20,25,26] Patients with generalized patch/plaque disease (stage IB, IIA) have a mean survival of 11 to 12 years, with around 20% progression of the disease to advanced stages. Patients in stages T3 (skin tumors) or T4 (erythroderma) have a worse prognosis with a mean survival of 1 to 5 years.[25,27] Prognosis is even worse for patients who develop extracutaneous disease and their mean survival is 1.5 to 3 years.[20,24]

Therapeutic strategies are primarily based on the clinical stage, for which the following studies are needed:

- Complete skin examination
- Peripheral blood evaluation for Sézary cells, preferably phenotyping using flowcytometry
- imaging studies to assess lymphadenopathy and visceral involvement[24,27,28]
- Lymph node biopsy—indicated only for clinically abnormal lymph nodes (>1.5 cm/day), with preference being given to the largest or the node with the greatest standardized uptake value on fluorodeoxyglucose positron emission tomography imaging[19]
- Bone marrow biopsy—considered only where bone marrow involvement is suspected, (eg, in Sézary syndrome)
- Polymerase chain reaction test for clonal rearrangement of the *TCR* gene. It has been incorporated in the last revision of the ISCL/EORTC classification of PCLs because it is considered as an adverse prognostic factor.[25,29-32]

In light of the current COVID-19 pandemic, initial staging remains important because it has a direct impact on the decision on therapy. Some additional procedures in CTCLs' staging, which are not indispensable for the choice of treatment choice, such as a lymph node biopsy, may be postponed.[18]

Table 4 Classification of PCL therapies based on the associated risk of COVID-19 complications.[15]

Level of risk	Therapeutic modality
Low risk	Topical retinoids, mechlorethamine gel or ointment, topical steroids with or without occlusion, imiquimod, home narrowband ultraviolet (UV) B phototherapy, heliotherapy, oral antimicrobials, oral antipruritics, dilute vinegar or bleach soaks/baths, and aggressive moisturization
Intermediate risk	Oral retinoids (bexarotene, acitretin, isotretinoin), methotrexate, oral steroids, vorinostat, and interferons (alfa or gamma)
High risk	Pralatrexate, romidepsin, mogamulizumab, brentuximab, gemcitabine and other chemotherapies, skin radiotherapy, phonophoresis, and office-based UV therapy (because of travel)

PCL, primary cutaneous lymphoma.

CTCLs other than MF/SS

Currently a new TNM staging system has been proposed for CTCL other than MF/SS.[33] This system is primarily indicated for measuring the tumor burden, but it has not prognostic value due to the heterogenicity of the group. Similar recommendations for staging in this group apply as in MF/SS. Staging procedures should be performed if they are directly related to the choice of treatment. A lymph node biopsy should be postponed unless it is required for therapy.[18]

Treatment of CTCLs during COVID-19

In COVID-19–negative patients, the treatment of PCL should be carefully reconsidered, because some therapies may pose additional complications, such as subsequent infection with the SARS-CoV-2 virus. In case of polymerase chain reaction–confirmed COVID-19 in a patient with PCL, priority should be given to treating the infection in a specialized COVID unit.[19] Subsequently, the PCL should be handled according to the following recommendations.

Generally, the treatment choice is based on the type of lymphoma, its clinical behavior, and the prognosis.[34] The choice is driven by the major prognostic factors, TNMB classification, and the clinical stage, as well as the MF variant (eg, folliculotropic MF) and the presence of large-cell transformation in the histologic specimen. Additional considerations could include the efficacy and toxicity of previous therapies, duration of the therapeutic response, comorbidities, accessibility, and cost-benefit.[27]

In the era of COVID-19, the selection of the treatment for PCLs should be additionally influenced by the potential effect of the therapy on the course of COVID-19 in case of infection. According to the US Cutaneous Lymphoma Consortium recommendations for treatment of cutaneous lymphomas during the COVID-19 pandemic,[15] therapies for PCLs could be classified into low risk, intermediate risk, and high risk for complications of potential concurrent viral infection with SARS-CoV-2. Data are summarized in Table 4.

Early-stage MF

Most patients with MF present with limited patch/plaque disease and may be managed either by the "watch and see" approach (the so-called expectant management) or by local therapy. Existent guidelines have encouraged patients to be managed during the pandemic by teledermatology, wherever possible, to avoid hospital visits and unnecessarily potential exposure to the virus.[16]

The preferred treatment for early-stage MF is skin-directed therapies. They are associated with low toxicity and are not inferior in efficacy compared with combined modality therapy, such as radiation therapy and multiagent chemotherapy (cyclophosphamide, etoposide, doxorubicin, vincristine, etc) for becoming disease free or overall survival.[35]

Generally, skin-directed therapies are considered low risk for potential complication of COVID-19 and should be continued at home during the pandemic. Only low-risk therapies are indicated for low-risk MF during the pandemic.

Low risk therapies for MF include the following:

- **Phototherapy**

  Phototherapy is considered low-risk therapy, and it is advised during the COVID pandemic; however, office-based phototherapy, which is one of the preferred treatment modalities for early MF, may be related to the patient's travel and associated risk for exposure to the novel coronavirus. Because this potential risk may outweigh the benefit of treatment, heliotherapy or narrowband ultraviolet (UV) B therapy could be initiated or continued only if home based.[15] In some countries the phototherapy units have experienced temporary closure during the peak of the pandemic due to prevention of potential in-hospital spread of the virus by outpatients or transformation of some dermatologic units into COVID-19 treatment sites.

- **Topical treatments**

  The use of topical treatments such as corticosteroids and mechlorethamine (available in some European countries) is encouraged.[16]

Advanced MF/SS

The real challenge during the COVID-19 pandemic remains the management of the advanced and aggressive forms of cutaneous lymphomas, including late-stage MF/SS. From one point of view, if left untreated, these patents are at a higher risk of developing complications in case of coronavirus infection due to their advanced malignancy. From the other, the treatment may be an independent risk factor. The benefits and risks should be discussed for each case individually before initiation of any new therapy.

Data show that patients with PCLs with well-controlled disease experience fewer infections than untreated patients. According to the current guidelines for management of late-stage or aggressive lymphomas during the coronavirus pandemic,[16], patients should receive timely appropriate treatment to prevent worsening of the disease and to avoid the complications in case of potential infection.[36]

We do not recommend prophylactic interruption of therapy, once initiated. When there has been a partial remission or the disease has been stabilized, it may be prudent to lower the dose or decrease the frequency of treatments, especially for patients with severe comorbidities and/or older age.[16]

Intermediate-risk therapies

According to the recommendations of the US Cutaneous Lymphoma Consortium, intermediate-risk therapies may be continued with individual adjustment of the dose. Initiation of these therapies should be ideally postponed by using a low-risk bridge therapy for a short duration. Intermediate therapies could replace, where possible, other high-risk therapies.[15]

- **Bexarotene**

  Bexarotene (oral retinoid binding to the retinoid X-receptor) is usually administered at a dose of 300 mg/m^2, which provides an optimal risk-benefit ratio. In clinical practice the drug is usually started at a lower dose (150 mg/m^2) with subsequent titration of the dose to 300 mg/m^2 within the first month of therapy. Treatment with bexarotene should be continued for up to 6 months to assess its efficacy, in case of lack of disease progression or toxic reactions.[19] The most common side effects include hypertriglyceridemia (in 82%) and central hypothyroidism (29%).[37] Adjunctive psoralen plus UVA or interferon may be considered.[38] Bexarotene is considered an intermediate-risk therapy during the COVID-19 pandemic,[15] and its ongoing application should not be discontinued.[16]

- **Interferons**

  Interferon alfa-2 (ie, interferon alfa-2b) is a type I interferon with immunomodulatory effects and with pleiotropic action in CTCLs. It is considered as second-line therapy in limited-stage CTCL and first-line treatment for advanced disease. Dose ranges from 3 to 10×10^6 units daily to three times weekly.[19,39] Treatment with interferon alfa-2 may be combined with psoralen plus UVA, bexarotene, chemotherapy, and extracorporeal photopheresis (ECP).[40-47] The main side effects include myelosuppression and flu-like symptoms, which are particularly associated with higher doses.[19] In the current pandemic, interferon alfa-2 is considered an intermediate-risk therapy,[15] and because the benefits generally overcome the risks in case of potential infection with coronavirus, we recommend that its administration should be continued.[16]

- **Methotrexate**

  Methotrexate is regarded as intermediate-risk treatment,[15] and it may be temporarily discontinued. This is arbitrary because supporting data are not available.

- **Oral steroids**

  Oral corticosteroids are regarded as intermediate-risk therapy during the COVID-19 crisis.[15] Consideration should be given to steroid-induced immunosuppression that may be prolonged, with normal immunity function expected to be delayed.[16]

High-risk therapies

The US Cutaneous Lymphoma Consortium suggests that infusion high-risk therapies should be adjusted to increase treatment intervals.[15] Alternative lower-risk therapies should be considered whenever possible.

- **Gemcitabine**

  EORTC Cutaneous Lymphoma Task Force guidelines[16] suggest treatment with gemcitabine be continued, despite the drug being labeled as high-risk therapy.[15]

- **Extracorporeal photopheresis**

  During the ECP, products from the plasmapheresis and the leukapheresis are exposed to 8-methoxypsoralen and subsequently irradiated with UVA. Finally, they are reinfused in the blood circulation. The result is apoptosis in the majority of the treated leukocytes, in association with activation of monocytes and dendritic cells' differentiation, which triggers a host immune response.[48,49] ECP is considered a first-line therapy for Sézary syndrome.[50] ECP is usually performed on 2 consecutive days every 2 to 4 weeks.[19] EORTC Cutaneous Lymphoma Task Force guidelines[16] suggest that ECP should be continued, despite the procedure being labeled as high-risk therapy during the COVID-19 pandemic.[15]

- **Brentuximab vedotin**

  Brentuximab vedotin (BV) is a conjugate, where an anti-CD30 antibody is linked with an antitubulin agent. Clinical trials report high efficacy of BV in advanced refractory MF/SS.[51] Even though considered high-risk therapy for potential complications according to the US Cutaneous Lymphoma Consortium recommendations,[15] guidelines[16] advise to continue treatment with BV during the pandemic. According to other recommendations, an effort could be made to extend the interval between treatments to reduce potential exposure to the virus during in-hospital visits.[18]

- **Mogamulizumab**

  Mogamulizumab (anti-CCR4 antibody) is considered as a high-risk therapy for COVID-19 complications because it is known to induce lymphopenia.[15] This agent could be considered in individual cases, with a lower dose and adjusted longer treatment intervals.[15]

- **Alemtuzumab**

  Alemtuzumab is a humanized immunoglobulin G monoclonal anti-CD52 antibody. The CD52-antigen is expressed on the surface of T cells, B cells, and monocytes.[52] The drug is intended for advanced-stage MF/SS.[53] A significant risk for infectious complications has been reported in patients who receive alemtuzumab subcutaneously, and the risk is dose dependent.[53-56] Infectious complications have been reported in up to two thirds of the treated patients, including bacterial, fungal, and viral infections.[19] Alemtuzumab is among the highest-risk therapies in terms of potential negative impact on the course of infection with SARS-CoV-2, due to its adverse effects, such as severe lymphopenia and immunosuppression. During the pandemic, its use should be limited whenever possible.[15]

- **Polychemotherapy**

  Conventional systemic chemotherapy rarely produces durable results in CTCLs.[57] More than 90% of CTLC patients treated with chemotherapy would require another therapy within 1 year of completion.[19] Polychemotherapy should be reserved for patients with massive tumor burden and/or visceral involvement who require rapid tumor debulking. Combination chemotherapy in MF/SS is associated with significant myelosuppression and infectious complications.[58,59] Polychemotherapy is regarded as high-risk therapy to produce adverse outcomes in potential coronavirus infection due to the high level of immunosuppression that it may induce. Its use is strongly discouraged during the pandemic.[15]

- **Clinical trials**

  Several ongoing clinical trials are evaluating the efficacy and safety of immune checkpoint inhibitors, such as pembrolizumab, in relapsed/refractory MF and SS. The major concern is hypersensitivity pneumonitis, which is associated with coronaviral infection.[60] Immune checkpoint inhibitors, which are currently being tested for treatment of advanced MF/SS and immunotherapy with PD-1 and PDL-1 increase the risk of autoimmune events, including pneumonitis. The management of these events usually requires high doses of corticosteroids. According to the current guidelines, it may be reasonable to temporarily interrupt these treatments in symptomatic patients with PCLs.[16]

- **Hematopoietic stem cell transplantation**

  Durable responses are reported after allogenic stem cell transplantation, which is probably due to the graft versus lymphoma immune response.[61,62] In selected patients it may be considered in conjunction with total skin electron beam therapy.[39,63] This procedure is strongly discouraged during the COVID-19 pandemic.[15]

CTCLs other than MF/SS

The same considerations for choice of therapy apply to patients with CTCLs other than MF/SS as for the MF/SS group. Therapy should be initiated with precaution in regard to the potential immunosuppression.

Cutaneous anaplastic large-cell lymphoma ($CD30^+$ CTCL) initially should be treated locally with surgical excision or radiotherapy. In case of dissemination or systemic involvement, systemic therapies are required.[64]

In cases of $CD30^+$ lymphoproliferative disorders (cutaneous anaplastic large-cell lymphoma and lymphomatoid papulosis), studies have reported high efficacy of BV, with a 74%[51] to 100%[65] response rate at week 12 and mean duration of treatment until response 3 weeks[65]; however, BV should be used with caution during the COVID-19 pandemic.[18]

Management of cutaneous B-cell lymphomas

Diagnostic approach to CBCLs during COVID-19

Generally, the diagnosis of CBCLs is made on the basis of histopathologic examination of a biopsy from a representative skin lesion. Additional immunohistochemical staining may be needed. The diagnostic approach to CBCLs includes also bone marrow biopsy, which is optional in primary cutaneous marginal zone lymphoma (Figure 6) and primary cutaneous follicular center lymphoma (Figure 7) and obligatory in primary cutaneous large B-cell lymphoma, leg type.[66] Additional studies include serum and urine immunoelectrophoretic testing and serologic testing for *Borrelia*.

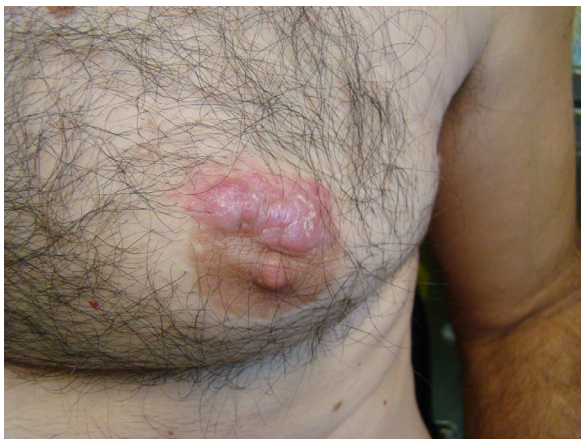

Figure 6 Primary cutaneous marginal zone lymphoma.

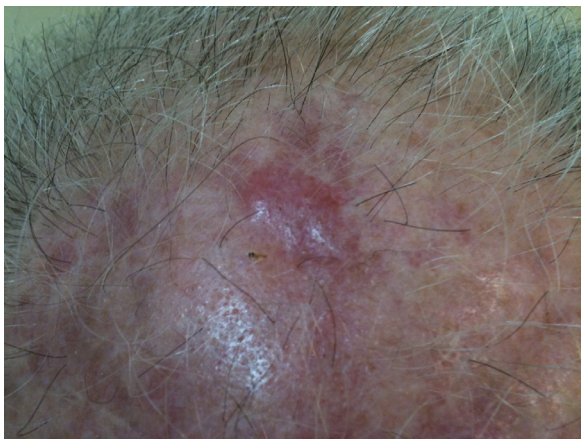

Figure 7 Primary cutaneous follicular center lymphoma.

The recommendations regarding the diagnostic of CBCLs during the COVID-19 pandemic are the same as for the CTCLs. These include a timely initial diagnosis.[18]

Staging of CBCLs during COVID-19

Routine staging for primary cutaneous marginal zone lymphoma and primary cutaneous follicular center lymphoma include whole-body computed tomography, positron emission tomography–computed tomography, and lymph node ultrasound. Additionally, magnetic resonance imaging of the affected extremity is suggested in primary cutaneous large B-cell lymphoma, leg type.[67] As for the CTCLs, recommendations suggest that initial staging remains important, whereas subsequent staging procedures for low-risk indolent CBCLs may be postponed for safety reasons to minimize the potential exposure to SARS-CoV-2 if there is no sign of disease progression.[18]

Therapy of CBCLs during COVID-19

According to the recommendations, the threshold for initializing systemic therapy in patients with indolent low-risk CBCLs should be high.[18] Watchful waiting is the recommended strategy to decrease potential exposure to the novel coronavirus during hospital visits or a more complicated clinical course in case of infection.

Generally the CBCLs with an indolent clinical course (primary cutaneous marginal zone lymphoma and primary cutaneous follicular center lymphoma) are managed by local therapy, including surgical excision or radiotherapy,[64] although the latter is considered a high-risk therapy during the COVID-19 pandemic.[15]

Interferons (an intermediate-risk therapy) are only rarely used in patients with CBCLs. Polychemotherapy is indicated only in cases of extracutaneous spread.[64] In disseminated or aggressive CBCLs, the initiation of therapy should be carefully weighed against the potential risk for iatrogenic immunosuppression.

- **Rituximab**

  Following the guidelines, patients with disseminated B-cell lymphoma, indicated for treatment with rituximab (anti-CD20 antibody), can postpone the treatment with 2 months; however, rituximab is not considered to have a potential negative effect on the COVID-19 disease course because it is reducing the B cells, whereas the production of immunoglobulins from plasma cells is maintained.[16]
  Patients with aggressive B-cell lymphoma should continue their treatment with rituximab during the pandemic.[19]

Impact of COVID-19 pandemic on PCL management in general

The COVID-19 pandemic has inevitably modified some aspects of PCLs management. PCLs are currently classified according to their susceptibility for infection, and treatment decisions are taken accordingly. In case of infection with SARS-CoV-2, prognosis of PCLs depends on disease type. Practical and logistic issues that arise during the pandemic provoke delays in diagnosis and a number of modifications in staging that should ensure the optimal evaluation of disease activity, while avoiding unnecessary procedures with increased exposure to the virus.

General recommendations

General recommendations for all patients with PCLs during the COVID-19 pandemic are prophylactic[19]:

- Self-isolation
- Social distancing
- Strict hand hygiene[68]
- Maintenance of skin integrity
- Compulsory masks

Conclusions

The majority of the patients with PCLs have an indolent course of the disease and are not at a higher risk of developing complications from viral infections than the general population, including infection with the new coronavirus. General measures for reducing the risk of acquiring the infection should be considered for those patients by reducing the frequency of hospital visits, the use of teledermatology, and preference of home-based treatments.

For patients with advanced and more aggressive forms of PCLs, who usually have multiple risk factors for a severe course of SARS-CoV-2 infection (older age, immunosuppression, multiple comorbidities, etc), therapy should aim at stabilizing the lymphoma with minimal risks associated with the treatment. The critical patient subset includes those with advanced disease, who require treatment with monoclonal antibodies, polychemotherapy, or checkpoint inhibitors. These decisions should be made on an individual basis.

A special consideration is the potential risk of hypersensitivity reactions related to the administration of drugs for advanced MF/SS, currently in clinical trials, which may aggravate COVID-19-associated pneumonitis.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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