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Histopathology as a key to identify Sézary syndrome in patient with clinical erythroderma

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ABSTRACT

Sézary syndrome (SS) is a rare and aggressive variant of cutaneous T-cell lymphoma (CTCL), characterized by clonal proliferation of malignant T lymphocytes with skin erythroderma. The incidence of CTCL in the United States from 2000 to 2010 reached 10 cases per million people per year, accounts for only 3% of all cases of cutaneous lymphoma. In Indonesia, lymphoma ranks sixth in terms of malignancies, alongside Hodgkin lymphoma and leukemia. We reported a case of 56 y.o. woman presented with blistering lesions that turned into wounds all over her body. Skin biopsy examination revealed characteristic histopathological features, including basket weave-type orthokeratosis, focal parakeratosis, focal acanthosis, and epidermotropism of atypical lymphoid cells with cerebriform nuclei (Sézary cells). Immunohistochemical examination using CD3, CD4, and CD8 showed positive staining in the membrane and cytoplasm of tumor cells within the dermis and epidermis. Sézary syndrome is characterized by clonal expansion of T-helper memory cells in the skin. Histopathology and immunohistochemistry could not differentiate SS from mycosis fungoides. However, histopathological examination could distinguish SS from other differential diagnoses. The diagnosis of SS can be established based on the triad of 1) generalized exfoliative dermatitis involving more than 80% of the body surface area, 2) lymphadenopathy, and 3) the presence of 5% or more malignant T-cells with cerebriform nuclei (Sézary or Lutzner cells) in peripheral blood lymphocytes. In conclusion, we present a case of SS, diagnosed based on the patient's history, physical examination, peripheral blood examination, histopathology, and immunohistochemistry.

ABSTRAK

Sindrom Sézary (SS) adalah varian langka dan agresif dari limfoma sel T kutaneus (*cutaneous T-cell lymphoma*/CTCL), yang ditandai oleh proliferasi ganas klonal limfosit T dengan eritroderma kulit. Insidensi CTCL di Amerika Serikat pada tahun 2000 – 2010 mencapai 10 kasus per satu juta orang per tahun, dan hanya terjadi dalam 3% dari semua kasus limfoma kulit. Di Indonesia, limfoma termasuk dalam peringkat keenam keganasan, bersama dengan limfoma Hodgkin dan leukemia. Kami melaporkan kasus seorang wanita berusia 56 tahun dengan keluhan lepuh yang pecah menjadi luka hampir di seluruh tubuhnya. Pemeriksaan histopatologi biopsi kulit mendapatkan sel limfoid atipi dengan inti *cerebriform* (sel Sézary) pada epidermis dan pada dermis atas yang tersusun secara *band-like*. Pada pemeriksaan imunohistokimia dengan pengecatan CD3, CD4, dan CD8 tampak sel limfoid atipik pada epidermis (epidermotropisme) dan membentuk pola *band-like* di dermis. Sindrom Sézary ditandai oleh ekspansi klonal sel memori T-helper di kulit. Histopatologi dan imunohistokimia tidak dapat membedakan SS dari mikosis fungoides, namun, pemeriksaan histopatologis dapat membedakan SS dari diagnosis banding lainnya. Diagnosa SS dapat ditegakkan dengan trias, yaitu 1) dermatitis eksfoliatif generalisata yang melibatkan lebih dari 80% luas permukaan tubuh, 2) limfadenopati, dan 3) keberadaan 5% atau lebih sel T ganas dengan inti cerebriform (sel Sézary atau Lutzner) dalam limfosit darah perifer. Sebagai kesimpulan, dilaporkan satu kasus sindrom Sézary yang ditegakkan berdasarkan anamnesis, pemeriksaan fisik, pemeriksaan darah tepi, histopatologi dan imunohistokimia.

Keywords:
malignancy;
cutaneous T-cell lymphoma;
Sézary syndrome;
epidermotropism;

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INTRODUCTION

Sézary syndrome (SS) is a rare and aggressive form of cutaneous T-cell lymphoma (CTCL). Sézary syndrome is characterized by malignant proliferation of clonal T lymphocytes that cause erythroderma, which is generalized erythematous and peeling of the skin. The incidence of CTCL in the United States is around 10 cases per million people every year, and SS represents only approximately 3% of all skin lymphomas. Based on medical records from Dr. Sardjito General Hospital Yogyakarta for the period of 2018 - 2022, 7 cases of CTCL were diagnosed, consisting of 5 cases of mycosis fungoides, 1 case of SS and 1 case of other types of CTCL, which histopathologically confirmed. SS has a poor prognosis with an average survival rate of around 5 years.[1] CTCL consists of several heterogeneous subtypes with different clinical findings, including mycosis fungoides (MF) and other variants. The more aggressive subtype is SS, which is often identified based on its histopathological characteristic appearance.[2,3]

This case report provided an understanding of the clinical and histopathological features of SS, so that it can help clinicians in better recognizing and diagnosing SS. This case is unique due to its initial misdiagnosis as a drug allergy following recent surgery, which delayed the recognition of SS. Additionally, this is one of few reported SS cases in Indonesia, making it an important contribution to the regional understanding of this rare disease. With a better understanding of the characteristics of SS, it is hoped that the handling and management of patients with SS can be improved.

CASE

A 56 y.o. woman presented to the Emergency Room of Dr. Sardjito General Hospital, Yogyakarta with her skin peeled almost of the whole body. Two months before admission, the patient had undergone appendicitis surgery. Three weeks later, reddish rashes appeared almost all over her body accompanied by swelling, followed by dehiscence of the surgical wound and the patient was diagnosed with suspected drug allergy (suspected caused by cefadroxil or ceftriaxone or sodium diclofenac). The patient was then admitted and the complaints were resolved. Two weeks later, skin peeling began to appear almost all over her body, accompanied by the dry skin appearance. Three days prior to admission, the patient felt noticed some blisters, some of which ruptured into wounds. The day on admission, peeling skin was affected almost all her body surface.

On physical examination, the general condition was good, compos mentis, with normal vital signs accompanied by enlarged cervical lymph nodes. On dermatovenereology examination, almost the entire body surface had erythematous patches covered with blackish scales. Ulceration and crusting were seen on the mucosa of the lips (FIGURE 1).

On supporting examination, positive Sézary cells were obtained from peripheral blood in three consecutive samples. The patient underwent a biopsy and histopathological examination. Histopathological examination of hematoxylin and eosin (H&E) stained slides found several specific condition in epidermis, including basket weave type orthokeratosis, focal parakeratosis, focal acanthosis, and epidermotropism of atypical lymphoid cells with cerebriform nuclei (Sézary cells) (FIGURE 2). In the upper dermis, an infiltration of atypical lymphoid cells with dense cerebriform nuclei was found, especially in the perivascular. Lymphocyte and neutrophil infiltrates were also obtained. In the immunohistochemical

examination with CD3, CD4 and CD8 staining, stained-positive results were obtained in the membrane and cytoplasm of atypical lymphoid cells with moderate to strong intensity. The histopathological examination and immunohistochemistry test in this case is in accordance with SS.

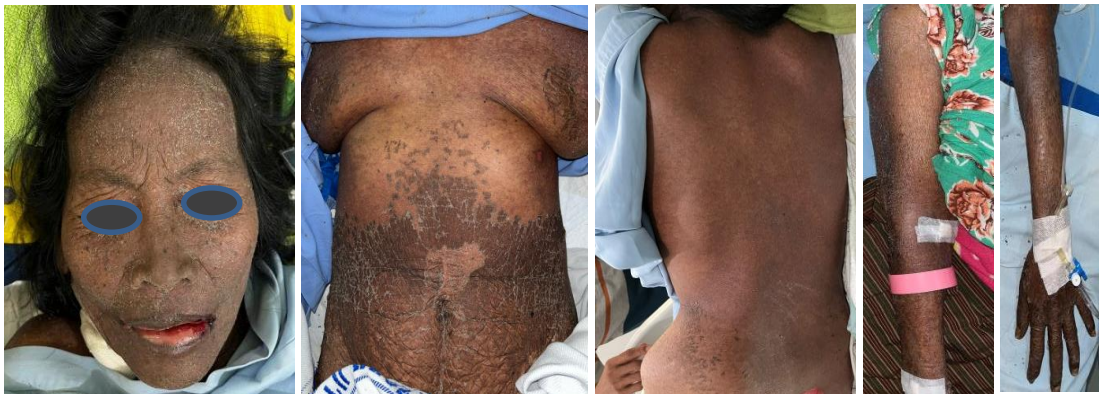

FIGURE 1. Erythema patches covered with blackish scales are found on almost the entire body surface.

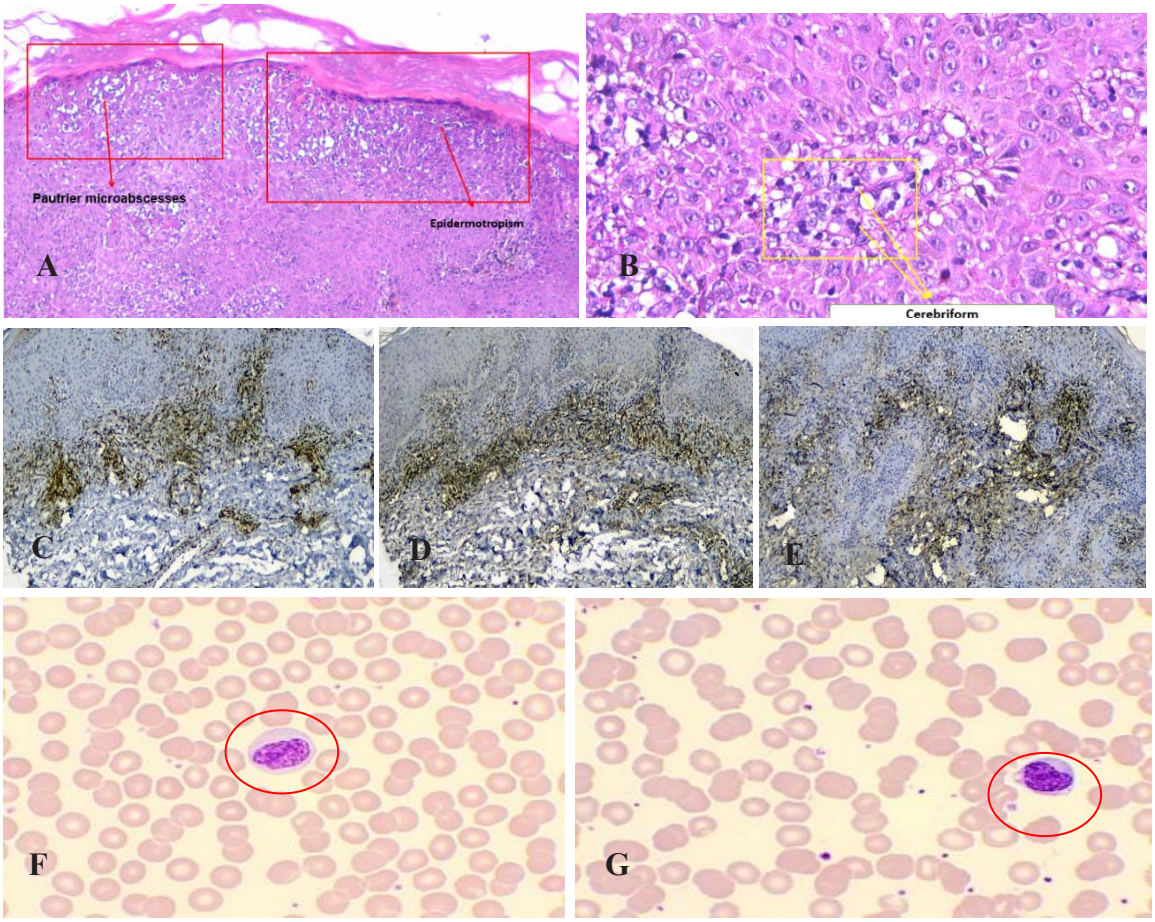

FIGURE 2. Histological examination of H&E and immunohistochemistry slides of the SS patient's specimen. (A) Pautrier microabcesses and epidermotropism (red arrow); (B) Cerebriform nuclei (yellow arrow); (C) CD3 staining, positive staining results with moderate to strong intensity in the membrane and cytoplasm; (D) CD4 staining, positive staining results with moderate to strong intensity in the membrane and cytoplasm; (E) CD8 staining, positive staining results with moderate to strong intensity in the membrane and cytoplasm; (F&G) Sézary cells from peripheral blood (red circle).

DISCUSSION

Sézary syndrome is a relatively rare type of CTCL characterized by clonal expansion of memory T-helper cells in the skin. Cutaneous T-cell lymphomas are a rare group of non-Hodgkin lymphomas (NHLs) characterized by the initial localization of malignant T cells in the skin. The current definition of these neoplasms according to the 2016 WHO classification of hematopoietic tumors and lymphoid tissues, which largely incorporates the WHO-EORTC classification for cutaneous lymphomas published in 2005.[4] The most common form of CTCL is mycosis fungoides, accounts for about 55% of cases. Sézary syndrome is much less common, accounting for only about 5%. Although the etiology of SS is unknown, many studies have been conducted to elucidate the underlying immunological pathways.[5]

The diagnosis of SS can be immediately established on subjective and objective findings, known as the Sézary syndrome triad, namely 1) generalized exfoliative dermatitis (affecting >80% of body surface area), 2) lymphadenopathy, and 3) the presence of 5% or more malignant T cells with cerebriform nuclei (Sézary cells) in peripheral blood lymphocytes. In addition, histopathological and immunohistochemical examinations can also be performed to establish the diagnosis of SS.[6,7]

Differential diagnoses according to the results of history based on physical and histopathological examination in this case were SS, Steven-Johnson syndrome (SJS), MF, and adult T-cell leukemia/lymphoma (ATLL). SS is characterized by erythroderma, which is redness on almost the entire surface of the skin. In some cases, the clinical presentation of SS can resemble SJS, a condition that is also characterized by a widespread skin rash that can turn into open wounds. Both syndromes have similar symptoms such as erythema, skin exfoliation, and possible involvement of internal organs. In MF, skin lesions may initially be erythematous patches localized in certain areas. However, in advanced stages, MF can develop into erythroderma. Erythroderma in MF generally has a slower rate of progression, and sometimes scaly lesions or plaques are seen in the erythroderma. While in ATLL, skin lesions are usually in the form of erythematous plaques, nodules to tumors, and very rarely become erythroderma.[3,8]

Blood test to detect Sézary cells is an important step in diagnosing SS and differentiate it from other conditions such as SJS and MF. Sézary cell blood tests analyze the lymphocyte cells in the patient's peripheral blood. In SS, an increase number of malignant T cells with cerebriform nuclei is known as Sézary cells. In MF, blood tests show an increase number of atypical lymphocytes that are sometimes difficult to be distinguished from Sézary cells. In this case, peripheral blood tests to confirm Sézary cells were performed with three consecutive samples. The results of these three consecutive tests showed positive Sézary cells, therefore excluding diagnosis of SJS and ATLL. The remaining possible diagnoses for this case were SS and MF.[7,9,10]

TABLE 1. Comparison of SS with Differential Diagnosis[3]

Case	Clinical manifestations	Histopathology
Sézary syndrome	Erythroderma	Epidermotropism (occasionally), atypical lymphoid cells (Sézary cells), Pautrier microabscesses
Mycosis fungoides	Patch, plaque, tumor	Epidermotropism, atypical lymphoid cells (mycosis cells), Pautrier microabscesses
Steven-Johnson syndrome	Epidermolysis	Keratinocyte apoptosis, lymphocyte infiltration
Adult T-cell leukemia/ lymphoma	Plaques, nodules, tumors	Epidermotropism, Pautrier microabscesses (predominant apoptotic fragments, atypical lymphocytes, and occasional pleomorphic nuclei)

Histopathology and immunohistochemistry are crucial to differentiate MF from SS. Histologically, SS shows features similar to advanced MF. In some cases, a superficial perivascular infiltration of atypical lymphocytes in the epidermis and dermis with epidermotropism was found and also Pautrier microabscesses. The main difference is the presence of large numbers of Sézary cells, atypical lymphocytes with convoluted or cerebriform nuclei. Sézary cells are often larger than the Mycosis cells seen in MF. In addition, MF has a higher frequency of epidermotropism and Pautrier microabscesses are also present.[3,9,11]

Immunohistochemistry in MF usually shows the expression of markers such as CD3, CD4, and often CD45RO. Other markers commonly expressed in MF include CD5, CD7, and sometimes CD8. Meanwhile, SS usually express markers such as CD3, CD4, CD45RO, and often lack CD7 expression. Loss of CD7 expression is a characteristic feature that can help distinguish Sézary cells from benign reactive T cells. The immunohistochemical pattern of SS usually includes CD3+ and CD4+ expression, with loss of CD7 and CD8- expression. This cannot distinguish it from MF. In addition, immunohistochemistry using the MUM-1 marker can assist the differential diagnosis between SS and MF. However, loss of CD7 by more than 50% of infiltrating T lymphocytes is an important criterion in supporting the histopathological diagnosis of SS. In this case, CD7 examination was not performed, so the presence or absence of CD7 expression could not be assessed. However, in this case, atypical cerebriform lymphocytes were found, so the more appropriate diagnosis is SS.[3,9,12]

It is important to note that histological and immunohistochemical findings must be interpreted in conjunction with clinical presentation, blood examination (presence of Sézary cells), and other diagnostic tests to establish a definitive diagnosis of SS or MF.[2,3] Clinical stage is a key determinant of disease progression risk and overall survival. For instance, a study in the United Kingdom found that advanced age was associated with a higher risk of disease progression, poorer overall survival, and worse disease-specific survival.[13] Similarly, a study in Florida reported a median overall survival of 5.2 years, with age over 65 years being a negative prognostic factor.14 Together, both the clinical findings and diagnosis were crucial in evaluating prognosis and planning individualized treatment strategies for Sézary syndrome.

TABLE 2. Comparison between previously reported cases of SS

Reference	Age (y.o)	Gender	Clinical Manifestations	Histopathology	Immunohistochemistry and CD4/CD8 ratio
Case	56	Woman	Generalized erythematous and scaly patches & lymphadenopathy	Epidermotropism, atypical lymphoid cells (Sézary cells)	CD3+, CD4+, and CD8+ CD4/CD8 ratio is not applicable
Tejashwini *et al.*[10]	48	Woman	Papules, erythematous patches & lymphadenopathy	Focal epidermotropism, atypical lymphoid (Sézary cells)	CD3+, CD4+, CD8- and CD26- CD4/CD8 ratio not applicable
Kamijo *et al.*[12]	49	Man	Symmetrical erythematous and purpuric papules	Epidermotropism, Atypical lymphoid cells (Sézary cells)	CD4+ and CD8- CD4/CD8 ratio of 19
Lynoora *et al.*[15]	60	Man	Pruritus, generalized erythematous nodules and alopecia	Focal acanthosis, dense lymphocytic infiltration	-
Miyashiro *et al.*[6]	83	Man	Erythroderma, alopecia, palmoplantar keratoderma, lower leg edema & weight loss	Atypical lymphoid cells, Pautrier microabscesses	CD4+ and CD8+ CD4/CD8 ratio not applicable

CONCLUSION

Although SS is very rare case, differential diagnosis should be considered when evaluating erythroderma with unknown cause. The diagnosis of SS in a 56 y.o. woman was established based on the presence of SS triad, namely generalized exfoliative dermatitis, lymphadenopathy and the presence of 5% or more malignant T cells with cerebriform nuclei (Sézary cells) in peripheral lymphocytes. In addition, it was supported by histopathological and immunohistochemical evaluation. Correct diagnosis is important in treating patients with SS.

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The authors declare no conflict interest of this case report.

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