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Idiopathic CD4⁺ Lymphocytopenia in Overlap Syndrome (Systemic Sclerosis with Dermatopolimyositis)

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ABSTRACT

Background: Idiopathic CD4 T cell lymphocytopenia (ICL) is a rare syndrome with varied clinical manifestation, characterized with lymphopenia and decreased in CD4 level without HIV infection or other possible cause of immunodeficiency state. Autoimmune diseases might be a clinical manifestation of ICL. However, it is not known whether ICL triggered an autoimmune diseases, or it is a complication of said diseases. **Objective:** Awareness of ICL in patient with known autoimmune diseases whom admitted to the hospital for severe infection. **Methods:** This case report showed a 24-years old woman with prolonged fever since 4 months ago. It was accompanied with oral ulcers, skin rash in face and trunks, and weakness of lower extremities. She was diagnosed with systemic sclerosis since 2016 and routinely came to rheumatology outpatient clinic in Hasan Sadikin Hospital but stopped coming for past 4 months since pandemic. Her current medication was only 4 mg of methylprednisolone. **Results:** She had high temperature (38.5 degree Celsius) and tachycardia. Physical examination revealed a single lymphadenopathy at neck. Raynaud phenomenon, calcinosis, and sclerodactyly was found in lower extremities. Dermatomyositis was diagnosed based by heliotropic skin rash. Laboratory tests showed leukopenia, absolute lymphocyte count 135.2 cell/mm³, absolute CD4 39/uL, CK level of 3296 and nonreactive anti-HIV. The patient underwent empirical antibiotic treatment, but unfortunately passed away. **Conclusion:** ICL is a rare case, following an infection, autoimmune diseases, or unspecified malignancy. Clinician's awareness toward ICL could prevent fatal opportunistic infection which often happens to patients with immunodeficiency state.

1. Introduction

ICL was found in 1980 and defined as a decreased in absolute CD4 count (less than 300) without any known infection, comorbid, or treatment-induced lymphopenia. It is a rare case, with only 24 cases was reported in range of 1993-2004.^{1,2}

We had a patient with known systemic sclerosis with newly found ICL.

2. Case

A 24-year old woman came to rheumatology outpatient clinic with continuous fever since 4 months ago. There was also painful ulcers inside her mouth. She experienced weight loss for the past 3

months, hyperemic skin rash which started from her face and spreading through her trunk and back. She also complained of weakness in all extremities.

She was diagnosed with systemic sclerosis since 2016 and routinely came to outpatient clinic in Hasan Sadikin Hospital. She used to consume metotrexate 12.5 mg once a week, methylprednisolone 4 mg once a day, folic acid 1 mg once a day, calcium carbonate 500 mg twice a day, nifedipine 10 mg twice a day, and aspilet 80 mg once a day. She had a history of tuberculosis treatment 8 years ago. Unfortunately since COVID-19 pandemic, she stopped coming to the clinic and only had

methylprednisolone 4 mg for almost 4 months. She was then admitted to the hospital.

She had fever (38.3oC) and tachycardia (108 bpm), otherwise within normal limits. Physical examination revealed anemic conjunctiva, pseudomembran oral ulcer inside her mouth, single painless lymphadenopathy at anterior neck, and existence of Raynaud phenomenon, sclerodactyly, and calcinosis in extremities. MRSS score was 9 and motoric examination score was 4 in all extremities.

Figure 1. Skin lesion in patient

Laboratory test showed hemoglobin 9,2 gr/dL, hematocryte 28,3%, Leukocyte 3.380/uL, thrombocyte 172.000/uL with absolute lymphocyte count 135,2 cell/mm³, ureum 12 mg/dL, creatinin 0,27 mg/dL, CRP 3,15 mg/dL, procalcitonin 0,2 mg/dL, LDH 1.352 mg/dL, Albumin 2,51 mg/dL, nonreactive anti-HIV, anti-HCV, and HbsAg, absolute

CD4 39/uL, and creatinin Kinase 3.296/uL. She also underwent a spirometry test which showed moderate restriction. HRCT scan showed patchy consolidation in almost all inferior lobe of left lung and poseterolaterobasal segment of right lung, suggesting an interstitial lung disease usual pneumonitic type, with active process and esophageal dilatation.

Figure 2. Thoracal HRCT scan in September 2020

In 2018 she underwent ANA examination, which revealed to be reactive with nucleolar pattern, 1:10.000 titer, ANA panel result was SSA positive, Panel SSc anti fibrillarin was positive. Skin biopsy result supporting the scleroderma. HRCT thoracal

scan conclusion was ground glass opacity and fibrosis in apicoposterior segment of superior lobe right lung. Patients was planned to have a PPD5TU, histoplasmin, and Cryptococcus LFA examination.

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FORMULIR HASIL PEMERIKSAAN LABORATORIUM

HS 08 B28 VII FM UM 017 Rev01

Patient ID: Ssc-II-018 Test: Systemic sclerosis (nucleoli) profile
 Patient name: Ssc-II-018 Lab number:
 Strip number: SSc/153-22 Receipt of sample:

Antigen	Intensity	Class	o (+)	+	++	+++
Scl-70	2	o				
Centromere A	1	o				
Centromere B	1	o				
RNA Pol III 11 kDa	2	o				
RNA Pol III 155 kDa	2	o				
Fibrillarin	41	++				
NOR90	3	o				
Th/To	3	o				
PM-Scl100	0	o				
PM-Scl75	1	o				
Ku	2	o				
PDGFR	1	o				
Ro-52	1	o				
Control	116	+++				

Intensity	Class	Explanation
0 - 5	o	Negative
6 - 10	(+)	Borderline
11 - 25	+	Positive
26 - 50	++	Positive
51 - 256	+++	Strong positive

Figure 3. ANA Panel in 2018

She was then diagnosed with prolonged fever e causa suspect disseminated fungal infection, hospital acquired pneumonia, limited systemic sclerosis with CREST syndrome and ILD overlap with dermatopolymyositis, suspect cutaneous B-cell lymphoma, and malnutrition.

The patient passed away after succumb to the infection.

3. Discussion

Patient came to the outpatient clinic after ceased to came because of pandemic. She only had 4 mg of methylprednisolon for the past 4 months. She came to the hospital with fever and rash throughout her face and trunks.

Patient was known to have systemic sclerosis since 2016, with ACR-EULAR 2013 score 21 and ANA-IF in nucleolar pattern, titer 1:10.000 with positive autoantibody SSA/antiRO and anti-fibrillarin. Both antibody was found in systemic sclerosis and related to incident of overlap syndrome

and interstitial lung diseases, both happens in this patient.³

Skin lesion was found 4 months before hospital admission. Skin lesion, weakness of extremities, and an increase of creatinine kinase showed a suspicious overlap syndrome with dermatopolymyositis. This patient did not met the mixed connective tissue criteria because we did not found specific autoantibody, anti U1-RNP dan U1-70 kd.⁴

The diagnostic criteria for dermatomyositis are:

1. Symmetrical muscle weakness with or without dysphagia or respiratory muscle weakness.
2. Increased serum skeletal enzymes, including creatinine kinase, aldolase, glutamate oxacetate, pyruvan transaminase and lactate dehydrogenase (LDH).
3. An electromyographic triad is found, that is, a short, small and polyphasic description of potential units; there is firbrillation with a positive sharp wave; and a high frequency, repetitive description of the action potential.

4. There are abnormalities from muscle biopsy with degeneration, regeneration, necrosis, phagocytosis and the presence of interstitial monoculcear cell infiltrates.
5. Characteristic features of skin lesions, including the presence of a heliotrope rash and Gottron's sign / papules.

Definitive diagnosis of dermatopolymyositis was 4 criteria, probable if there was 3 criteria, possible if there was 2 criteria. In other criteria, definitive diagnostic was a rash with 3 criteria, probable was a rash with two criteria, and possible if there was rash with 1 criteria.⁵ This patient was diagnosed with probable dermatomyositis.

Vijayakumar et al conducted a literature review about ICL. They found a defect n immunology system in ICL, with decrease of naïve T-cell, increased TCR stimulation, and decrease of TCR's repertoire. A few hypothesis of pathomechanism in CD4 decline was increase of apoptosis, genetical defect, cytokine dysregulation, sequestration of CD4, and immune senescens.⁶

Clinical manifestation of ICL is variable. The patients could be asymptomatic until admitted to the hospital for fatal infection. Most common involved organs were skins, central nervous systems, and lungs.⁷

Little to none was understood about ICL. Yarmohammadi et al found 34 case of ICL in the span of 22 years, 17 cases (71%) came with infection, 4 cases (17%) with malignancy, 8 cases (33%) with autoimmune disease, and 3 cases (13%) with unexplained demyelination.⁷ Cohort study by Ahmad et al towards 259 datas in 1989-2012 showed that 85 cases (33%) have autoimmune diseases.⁸

Very low CD4 count made the patient very susceptible to infection. Study showed that the main etiology of these infections were *C. neoformans*, *Mycobacterium*, and *Candida*.⁸ Our patient gene-expert examination for tuberculosis revealed to be negative and her blood cultures were also sterile.

Figure 4. Ten main opportunistic infection in ICL⁸

We had considered whether this was a side effect of immunosuppressive drug consumed by the patient. There was a study thath showed that 33% of patient consuming metrotrexate had a decline of CD4 count to less than 350, but the subject was an HIV

positive patient, which was not match with our patient.⁹

6. Conclusion

ICL is a rare condition and mostly found accidentally following a severe opportunistic infection, autoimmune diseases, or malignancy [490]. Lack of screening and awareness of this condition in autoimmune patients might worsen their condition, since immunosuppressant and immunomodulator which provide relieve and controlled their condition could aggravate the infection. Strict monitoring could prevent the progress of infection.

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