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MULTI-SYSTEM HISTIOCYTOSIS OF LANGERHANS CELLS IN BOYS AGED 2 YEARS (HISTOPATHOLOGY REVIEW)

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ABSTRACT

Langerhans cell histiocytosis (HSL) or histiocytosis X, eosinophilic granuloma, letterer siwe disease, hand schuller christian disease and hashimoto pritzker disease is a disorder caused by the accumulation and proliferation of langerhans cells in various organs of the body that causes tissue damage. The highest prevalence of HSL occurs in children less than 3 years old, with a ratio of 2:1 for boys and girls. The classic appearance of skin manifestations is an eruption resembling seborrheic dermatitis in the folds, axillae, scalp, retroauricular and trunk areas. The appearance of the lesion is yellow to brownish red papules, purpuric and crusted papules that can occur together with erosion. Histopathological examination with staining with S100 or cluster of differentiation 1a (CD1a) revealed Langerhans cell infiltration. The results of immunohistochemistry with IHC S-100 staining, CD1a showed a picture of Langerhans cells and histiocytes. The purpose of this paper is to study the histopathological features of HSL to better than to diagnosis and treatment of HSL. A 2-year-old boy was consulted with the chief complaint of itchy red nodules on the head, chest and back area. Complaints accompanied by diarrhea, often feel thirsty and hungry and lose weight. Dermatological status in the facial region, the anterior and posterior trunks showed lenticular papules with umbilication (pin points) with erosions covered with necrotic tissue above, on the scalp, facial, retroauricular and trunk regions, yellow to brownish papules were crusted with erosions. Histopathology with hematoxylin and eosin (HE) staining showed the presence of small fragments of skin tissue, the epidermis was partially composed intact, the dermis was filled with histiocytes, plasma cells, eosinophils, mast cell impressions and polymorphonuclear leukocytes. Immunohistochemical examination with staining IHC S-100 and CD1a showed positive. Histiocytosis is a group of disorders characterized by the accumulation of cells derived from dendritic cells accompanied by inflammation and causing tissue damage. Histopathological and immunohistochemical examinations serve to establish the diagnosis. The results of immunohistochemical examination with IHC S-100 staining, CD1a will show a picture of Langerhans cells and histiocytes.

Introduction

Langerhans cell histiocytosis (HSL) or histiocytosis X, eosinophilic granuloma, letterer siwedisease, hand schuller christian disease and hashimoto pritzker disease is an abnormality caused by the accumulation and

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proliferation of langerhans cells in various organs of the body that cause tissue damage (Kobayashi & Tojo, 2018). The etiology of HSL is still not known for certain and is a debate between neoplastics or inflammatory disorders (Morren et al., 2016). HSL pathogenesis is associated with somatic mutations, infection, immune system dysregulation or cytokines and apoptosis (Flego & Volaric, 2018).

Langerhans cell histiocytosis is the most common histiocytosis disorder, characterized by abnormal proliferation of histiocytes or progenitor cells in the bone marrow (Atmatzidis et al., 2017; Durham, 2019). The prevalence of HSL in the world is reported to be 2-9 cases/1,000,000/year that can occur at any age with the highest cases occurring in children younger than 3 years of age. (Jaffrain-Rea & Filipponi, 2021; Krooks et al., 2018). Ain Sham in 2020 in Egypt reported 37 cases of HSL (Jaffrain-Rea & Filipponi, 2021). Munthe et al in 1995-2002 at Cipto Mangunkusumo Hospital reported 14 cases of HSL.10 Boys were more likely to get HSL than girls by a ratio of 2:1. (Hutter & Minkov, 2016).

Manifestations of Langerhans cell histiosis can affect a wide variety of organs where most commonly involved are the skeletal system or bone, skin, pituitary or pituitary, liver, spleen, hematopoietic system, lungs and lymph nodes (Krooks et al., 2018). Enforcement of the diagnosis of HSL is based on clinical manifestations, histopathological examination and electron microscopy. The definitive diagnosis of HSL is obtained by examination of histopathological biopsy and immunofluoresensis.

Characteristics of histopathological examination in HSL are the discovery of morphology of birbeck langerhans cells or granules confirmed with immunofluoresensis protein S100 positive, antigen cluster of differentiation 1a (CD1a) or immuhistochemical langerin using electron microscopy (Munthe, 2016). Diagnosis appeals to Hailey-Hailey's disease and transient willtolytic dermatosis (Grover's disease). Histopathological description of Hailey-Hailey disease is disceratosis and will be suprabasilar healysis, especially in the spinosum layer, thus providing an image of the collapsed brick wall. Grover's disease suggests willtolysis in the suprabasal with disceratosis and eosinophilic spongiosis (Munthe, 2016).

Histiosis of langerhans cells that manifest in the skin generally improves spontaneously, but if it does not improve spontaneously we can give topical steroid therapy, methotrexate or thalidomid orally, topical mustard nitrogen or psoralen with UV light. (Uppal et al., 2012).

Langerhans cell histiocytosis is a rare disease, so there is often an error or delay in diagnosis. The purpose of writing this paper is to study the histopathology picture of HSL so as to better understand the enforcement of HSL diagnosis and the provision of appropriate procedures.

Methods

A 2-year-old male patient was consigned by the Child to the Skin and Genital section of Dr. Moewardi Hospital (RSDM) Surakarta on October 14, 2020 with the main complaints appearing reddish nodules on the head, chest and back areas. Six months before entering the hospital the patient experienced complaints of redness on the scalp that feels itchy and scaly. The patient was taken to a GP and then given a concoction drug but the name of the drug was not known and the complaints were felt to be improving. Five months before entering the hospital there are similar complaints accompanied by fever, patients go to a skin and genital specialist and given desolex cream® (desonide), mupirosin cream and syrricin. Complaints are felt to improve but when the drug runs out of nodules - redness in

the skin recurs. Four months before entering the hospital complaints are felt increasingly burdensome accompanied by an enlarged stomach, patients treated by a pediatrician is advised to be referred to rsdm because of suspected blood disorders. The patient's parents do not take the patient to rsdm but only treatment by taking herbal medicine. Complaints of patients gaining weight, namely redness in the skin are increasingly extended to the body, accompanied by diarrhea, often feeling thirsty and hungry and weight decreases. Patients are hospitalized by the child and consigned to the Skin and Genital Health section for joint treatment..

The patient was the fifth of five children with a history of motherly having two abortions (P5A2). Patients born at 39 weeks gestation are normally pervaginam in the hospital and cry strongly with a birth weight of 3500 grams with the mother's age when giving birth to a patient of 40 years. The basic immunization history is incomplete, the patient only gets immunized once at birth (hepatitis B0).

On the physical examination obtained the general condition of the patient appears moderate pain with compos mentis awareness. The patient's weight is 11 kg and height is 85 cm with poor nutritional status. Vital signs are obtained within normal limits. In the right and left ear secretes a dark brown liquid, solid and odorless consistency accompanied by enlargement of posterior auricular lymph nodes, enlarged liver and enlargement of the spleen. Dermatological status in the fascial regio, anterior trunkus et posterior appear papule lenticular accompanied by umbilication(pin point)with erosion and covered necrotic tissue above it, on the regio of the scalp, fascial regio, retroauricular regio and regio trunkus appear papule yellow to brownish that erodes accompanied erosion (Figure 1). Based on the results of anamnesis and physical examination, patients are diagnosed with langerhans cell histiocytosis (HSL), mastocytosis and seborrheic dermatitis.

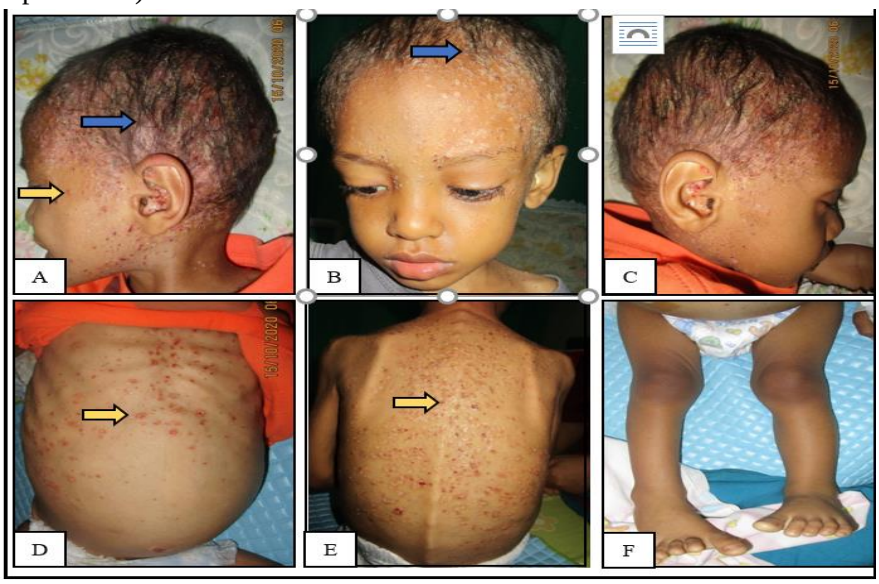


Figure 1

(A-F) In the fascial regio, the anterior et posterior trunkus appears to be a multiple lenticular erythular papule accompanied by umbilication (pin point) (yellow arrow) partially confluent with erosion covered in necrotic tissue above it, on the regio of the scalp, fasciast, retroauricular and trunkus appears yellow papules to brownish that erode accompanied by erosion (blue arrow)

Laboratory test results on October 12, 2020 showed an increase in leukocyte levels of 14.7 thousand / uL (4.5-11.0 thousand / uL), serum glutamic oxaloacetic transaminase (SGOT) 81 U / L (<45 U / L), serum glutamic pyruvate transaminase (SGPT) 48 U / L (<45 U / L) and gamma GT 589 IU / L (0-51 IU / L). Decreased hemoglobin 8.5 g/dL (12.0-15.6 g/dL), hematocrit 26% (33-45%), erythrocytes 3.45 million/uL (4.10-5.10 million/uL), albumin 2.4 g/dL (3.8-5.4 g/dL), alkali phosphate enzyme 1.1 65 U/L (40-129U/L), a blood sodium electrolyte of 131 mmol/L (132-145 mmol/L), 2.9 mmol/L (3.1-5.1 mmol/L), 106% (98-106%) blood chloride and 1.09% calcium (1.17-1.29%). Non-reactive HBsAg and platelets within the normal limit of 422 thousand / uL (150- 450 thousand / uL).

Ultrasound examination (ULTRASOUND) on October 15, 2020 found a picture of parenchymal liver disease hepatomegali, splenomegali and ascites, no abnormalities in the gallbladder, both kidneys and bladder. Koh's examination results on October 14, 2020 were negative. Histopathology examination on October 15, 2020 was carried out with a punch biopsy technique using plong no. 3.0, skin tissue taken from papule lesions in the anterior trunkus with coloring Hematoxylin Eosin (HE). The tissue is taken perpendicular to subcutaneous depth then soaked in a 10% formalin buffer solution.

Results and Discussions

Histiocytosis is divided into several types, depending on the origin of its progenitor cells such as langerhans cells, dendrosit dermis and mononuclear or macrophage cells that can be the cause. Langerhans cells are dendritic cells (SD) derived from the bone marrow and can be found mainly in the epidermis of the skin as well as on mucous membranes, thysous, esophagus and lungs. Histiocytosis of langerhans cells is characterized by the accumulation and proliferation of langerhans cells that cause tissue damage.

Research by Valerie Broadbent et al in 1993 at Harvard University Hospital and Clinic and East River Road, obtained HSL can occur at all ages with the highest age at the age of 1-4 years. The average patient with HSL is less than 3 years old. The incidence of HSL in children is 2-9 cases per 1,000,000 children per year while in adults 1-2 cases per 1,000,000 population. The incidence in men is more than that of women.13 In this case patients aged 2 years with male sex so that according to the literature.

The etiology of HSL is still unknown. Some hypotheses state that HSL is caused by somatic mutations, infection (especially viruses), cytokine dysregulation and apoptosis. Somatic mutations are the most HSL etiology. Mutations in the mitogen activated protein kinase (MAPK) pathway were found in 80% of HSL patients. Risk factors that can trigger the occurrence of HSL include hispanic ethnicity, in vitro fertilization, mothers who experience urinary tract infections during pregnancy, neonate infections, blood transfusions as infants, problems with low protein food intake, low education levels, living in crowded places, families with a history of thyroid disease. Factors that can protect against the incidence of HSL include black race, vaccination during neonates and administration of vitamin B9. In this case based on anamnesis there are no complaints of pain until the patient is 2 years old, neonate infection and history of transfusion when the baby is denied, the history of the mother suffering from pain during pregnancy is denied. In patients there is an incomplete history of immunization and a low level of parental education. This is thought to be the cause of risk factors in patients.

The classification of HSL is based on organ involvement i.e. when the disorder in

only one organ system is called single system HSL (SS-HSL) whereas if HSL involves two or more organ systems it is classified into multi-system HSL (MS-HSL). Skin involvement is a type of manifestation of HSL that is most often complained about because it is easily visible. Manifestations on the skin become the main manifestations found in children less than 2 years of age. Its classic look like an eruption resembles seborrheic dermatitis of the crease area, axila, scalp, retroeuricular and trunkus. The image of lesions in the form of yellow to brownish red papules, purpurik and eroded papules that can arise along with erosion. Palms and feet may be involved in some cases. In this case the patient has a skeletal disorder. Manifestations in the area of the scalp, fasciast, retroauricular and anterior et posterior trunkus in the form of yellow to brownish papules that are eroded by erosion of the above and posterior auricuous lymphadenopathy. Skin manifestations in these patients correspond to skin manifestations in patients with HSL. This patient has disorders of skeletal, skin, lymphadenopathy, involvement of at-risk organs such as enlargement of the spleen and liver, abnormalities in the endocrine system and hematopoiesis so that based on the classification of HSL this patient is included in the multi-system classification of HSL (MS-HSL).

Definitive enforcement of the HSL diagnosis is an examination with an electron microscope i.e. obtained birbeck granules and was once considered a gold standard for diagnosing HSL but this examination is rarely done because it is difficult to obtain a special dye. Routine histopathological examination to establish the diagnosis is immunohistochemical examination with staining S100, CD1a or langerin. (Pogorzelska-Dyrbuś & Szepietowski, 2020). The findings of langerhans cells with immunohistochemical staining using CD1a and S100 were used as definitive diagnoses of HSL. In these patients with electron microscope examination we do not do because of the limitations of the tool, but based on the criteria of clinical manifestations and supported histopathological examination in patients this patient can already be enforced diagnosis of HSL.

In histopathological examination of patients with the painting of Hematoxiline Eosin (HE) found the presence of small fragments of skin tissue, the epidermis partially arranged intact, dermis with a cell histiocyte, plasma cells, eosinophils, mast cell impressions and polymorfonuklear leukocytes. The results of the patient's histopathological examination in accordance with the theory of HSL image that is a partially intact epidermis and other parts there is parakeratosis, dermis there are round cells with a diameter of 15 - 25 microns with eosinophilic cytoplasm, indented nucleus or reniform, coffee bean and vesicular called histiocyte cells with a mixture of eosinophils and lymphocytes (Figure 5) (Patterson & Hosler, 2016). The histopathology picture of mastocytosis according to the theory is a whole epidermis with basal cell hyperpigmentation, dermis there is an accumulation of spindle-shaped or cube-shaped cells with eosinophilic cytoplasm and firmly bordered with a pale nucleus called mast cells and there is also edema papila dermis (Figure 6). Histopathological images in seborrheic dermatitis will show a picture according to the clinical course, in acute lesions appear mild spongiosis with a little netrophile in the epidermis, edema papillary dermis and superficial blood vessels that dilate with a little infiltration of lymphocytes, histiocytes and netrophiles. Subacute lesions on the epidermis show a picture of spongiosis and mild psoriasiform hyperplasia. Chronic lesions show a stratum corneum image of more pronounced psoriasiform hyperplasia

and minimal spongiosis, as well as focal parakeratosis (Figure 7) (Hamodat, 2011).

Immunohychemical examination is done because histopathology examination with the painting of Hematoxiline Eosin (HE) has not been able to get rid of the differential diagnosis. Immunohychemical examination results of patients with painting of S-100 and CD1a showed positive in some cells, a picture of Langerhans cells or Birbeck granules and brown histiocytes. The results of the patient's histopathological and immunohympychemical examinations fit the theory that HSL will be positive on examination by painting CD1a and S-100 and produces a picture of Birbeck granules and histiocytes as brown as tennis rackets with a zipper-like appearance (Figure 8) (Patterson & Hosler, 2016). In contrast to HSL, immunohychemical examination with coloring of toluidine blue, giemsa, monoclonal antibody and CD117 (KIT) will show the presence of mast cells (Figure 9) (DiCaprio & Roberts, 2014).

The implementation of HSL depends on the criteria of HSL classification in patients (Claire et al., 2020). Patients with SS-HSL on the skin are adequately observed. If skin lesions do not resolve spontaneously or severe skin lesions various methods may be used such as topical steroid administration for 4 weeks, oral methotrexate or thalidomide, topical mustard nitrogen and psoralen with UV light (Allen et al., 2018; Chen et al., 2020). Administration of systemic therapy regimens is indicated in SS-M patients(single system on multiple sites)with lesions involving the base of the skull and the involvement of adjacent soft tissues, temporal bones, orbits, vertebral bones and MS-HSL (multi-system HSL). (Haupt et al., 2013). Screening examination before being given procedures in HSL patients in the form of complete anamnesis should include symptoms specific to the nature and duration of symptoms and laboratory examinations. Special symptoms to look for are pain, swelling, skin rash, otorrhea, fever, loss of appetite, diarrhea, poor weight, failure to grow, polydiption, polyuria, respiratory symptoms, irritability, behavior and neurological changes, physical examination including growth parameters. Laboratory examinations are required before therapy (complete blood count, coagulation test, liver function test, urine osmolality), bone radiography, chest, bone marrow examination, lung function test, lung biopsy, dental panoramic, CT or MRI of the central nervous system and endocrine evaluation. Evaluation of therapy is done to prevent the occurrence of reactivation of the disease. Patients without the involvement of at-risk organs, although not at risk of death require systemic therapy to control disease activity, reduce reactivation and reduce the consequences of permanent disease. (Haupt et al., 2013).

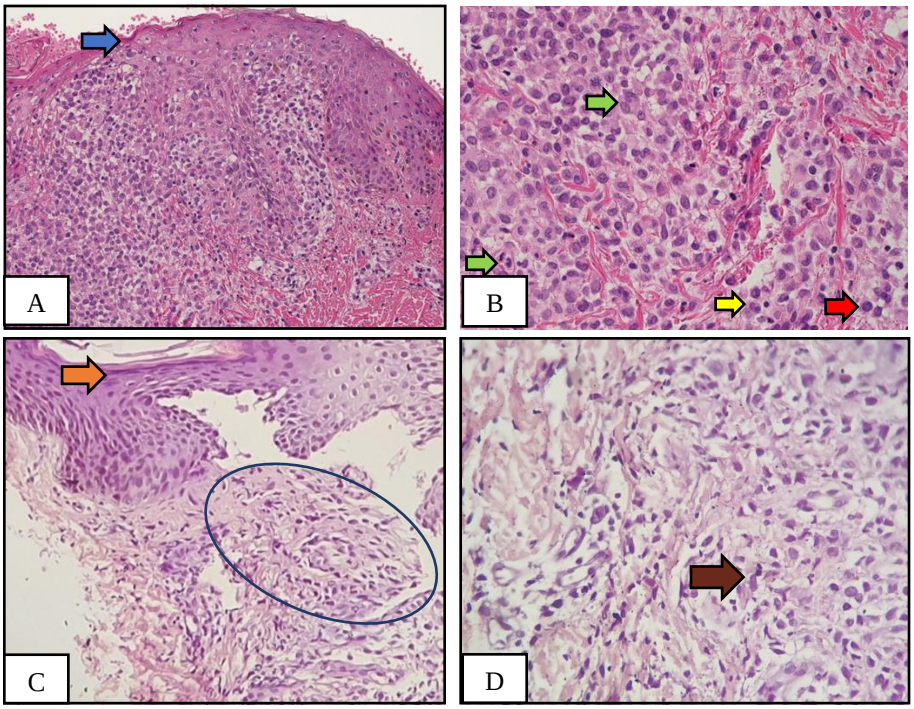
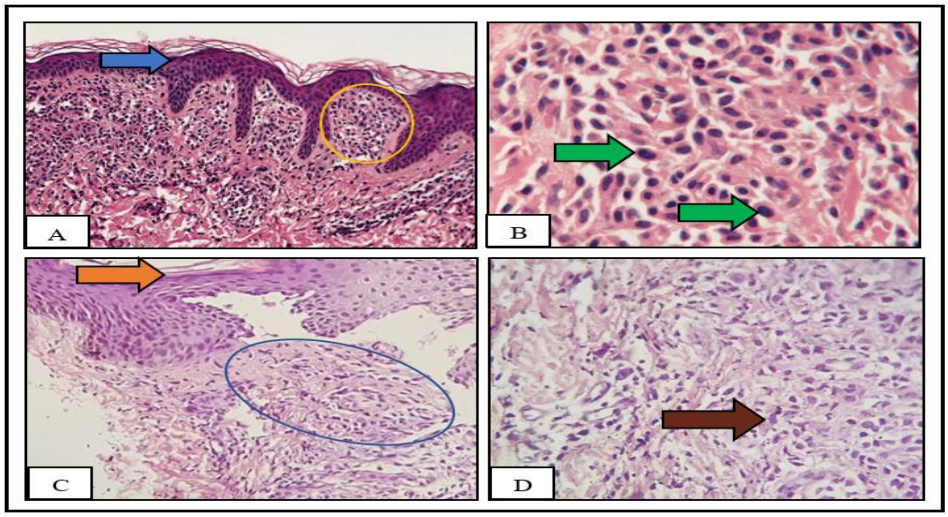


Figure 5

(A - B) HSL histopathology image on litelatur with coloring H&E. (A) The epidermal layer is arranged intact (blue arrow). (b) The dermis layer contains histiocyte cells (green arrows), eosinophils (yellow arrows) and lymphocytes (red arrows) (Weedons's skin pathology, 2021). (C - D) Histopathological description of patients with H&E. (A) Epidermal layer is composed of intak (people's arrows) and PMN leukocytes (blue circles). (b) Dermis there are lymphhisticytic cells (brown arrows), plasma cells, histiocytes, eosinophils, mast cell effects (HE magnification of 10x, 40x).

The standard systemic treatment recommended is the administration of steroids and vinblastin or methotrexate in the initial intensive phase for 6-12 weeks followed by maintenance therapy with a total duration of treatment of at least 12 months to reduce the risk of reactivation of the disease. Patients who do not respond to treatment are eligible for therapy with cladribin, cyarabin, klofarabin or a combination of such drugs as well as transplants of bone marrow and/or other organs. (Gadner et al., 2013). In this case the patient received therapy from the Child section in the form of systemic chemotherapy therapy with a 5 mg/week methotrexate injection and etopul® (etoposide) injection of 60 mg intravenous bolus/week for 6 weeks, prednisone tablets 40 mg/day 3 divided doses, klonidin tablets 0.15 mg/day, vip-albumin (Ophiocephalus striatus extract) tablets 3 times daily, minirin (desmopressin acetate) tablets 0.1 mg 3 times daily. On the skin provide topical therapy on skin lesions in the form of NaCl compresses 0.9% for 10-15 minutes on thick krusta area. Administration of mometason cream applied to the head, back and chest area as much as 2 times a day, gentamicin ointment applied 2 times a day on the erosionarea.



Gambar 6

(A - B) Histopathology image of mastocytosis in litelatur with coloring H&E. (A) The epidermal layer is intact with basal cell hyperpigmentation (blue arrow) and there is also edema papillary dermis (yellow circle). (b) The dermis layer contains an accumulation of spindle-shaped or cube-shaped cells with eosinophilic cytoplasm and a firm border with a pale nucleus called Mast cells (green arrows) (Weedons's skin pathology, 2021). (C - D) Histopathological description of patients with H&E. (C) Epidermal layers composed of intak (people's arrows) and PMN leukocytes (blue circles). (d) Dermis there are lymphhisticycytic cells (brown arrows), plasma cells, histiocytes, eosinophils, mast cell effects (HE magnification of 10x, 40x).

On the observation of the 30th day of treatment, there is an improvement in complaints of systemic abnormalities in the form of reduced itching, crucises thinning, papules eritem appear to be reduced. Patients go home in a state of improvement, evaluation of therapy by looking at systemic complaints and improvement of skin lesions divided into better if there is complete regression, intermediate i.e. there are lesions that regress and arise new and worse lesions that are increasingly progressive systemic lesions and abnormalities. If the response is good with the procedures given then this patient will be classified in patients with better or intermediate therapeutic response and the next tatalaksana plan is the administration of therapy by the Child with etopul injection® (etoposide) 60 mg intravenous bolus / week for 6 weeks and prednisone tablets 40 mg 3 divided doses for 3 days / week. Maintenance therapy up to 12 months with an intravenous injection of 60 mg intravenous bolus/3 weeks and prednisone tablets 40 mg 3 divided doses for 5 days / 3 weeks. Education in the patient's family is about the course of the disease (the purpose of treatment, expected treatment results, length of therapy, how to use drugs and possible side effects), the importance of skin care and avoiding treatment outside the prescribed, maintaining skin hygiene, diligently cutting fingernails and avoiding scratching that can cause irritation lesions and not using clothes that causeirritation.

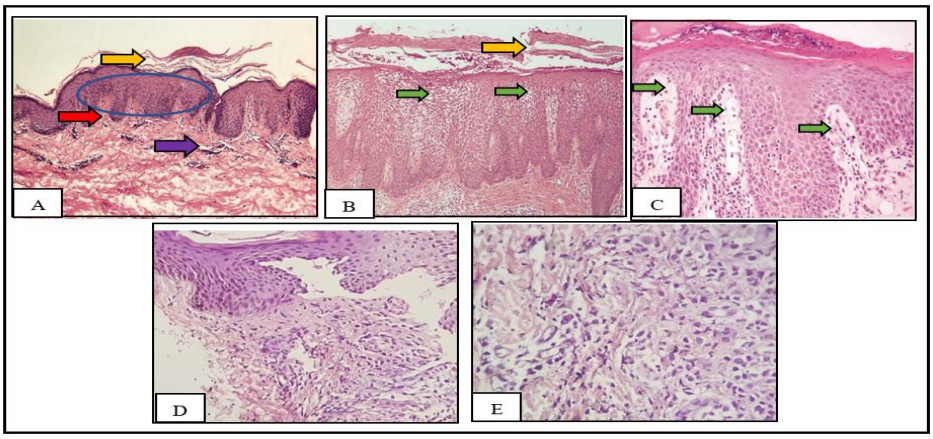


Figure 7

(A - B - C) Histopathological images of seborrheic dermatitis in litelature with H&E staining of the epidermis appear spongiosis (green arrow), parakeratosis (yellow arrow) and hyperplasia psoriasiform (blue circle). Edema of the dermis papillae (red arrow) as well as superficial blood vessels that dilate with slight infiltration of lymphocytes, histiocytes and netrophiles (purple arrows). (D - E) Histopathological description of patients with H&E. (D) Epidermal layers composed of intak (people's arrows) and PMN leukocytes (blue circles). (e) Dermis there are lymphhisticytic cells (brown arrows), plasma cells, histiocytes, eosinophils, mast cell effects (HE magnification of 10x, 40x)

In HSL involving bone or single skin lesions the prognosis is good, there are cases of spontaneous remission or symptoms subside after local treatment. Recurrence of the disease is more common when there is multifocal bone involvement. Cases of extensive skin lesions are likely to be internally involved to several years after the completion of the first-line treatment of the disease. The prognosis worsens significantly with the involvement of at-risk organs and GI channels, spontaneous regression is rare. Recurrence is one of the most important problems in the management of HSL, recurrence occurs in almost a third of patients. New bone lesions are the most commonly found at the time of recurrence. Jubran reported a seven times higher risk of reactivation for patients with multiple bone lesions compared to patients who had single bone involvement. (Jezierska et al., 2018). The prognosis of patients in this case is dubia ad night because spontaneous regression is rare and there are 2 or more systemic organs namely hepatomegaly and gastrointestinal tract involved. Proper therapy in the early stages of the disease is expected to reduce morbidity in patients, prevent reactivation, the emergence of new lesions and progressive systemic abnormalities.

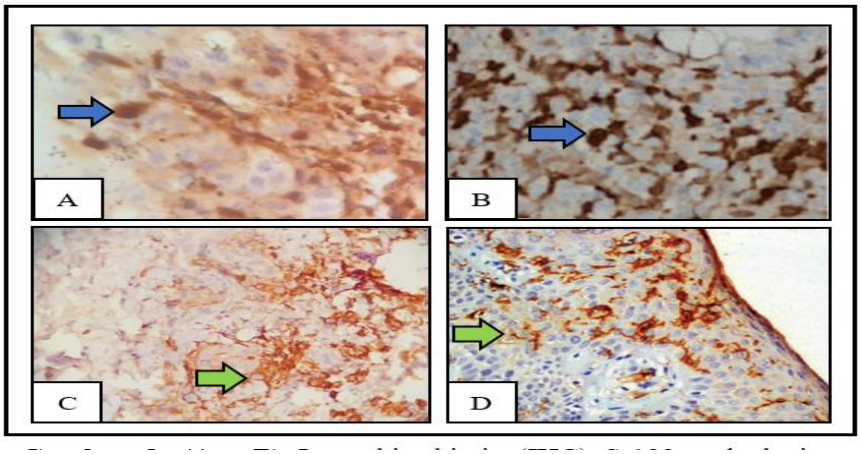
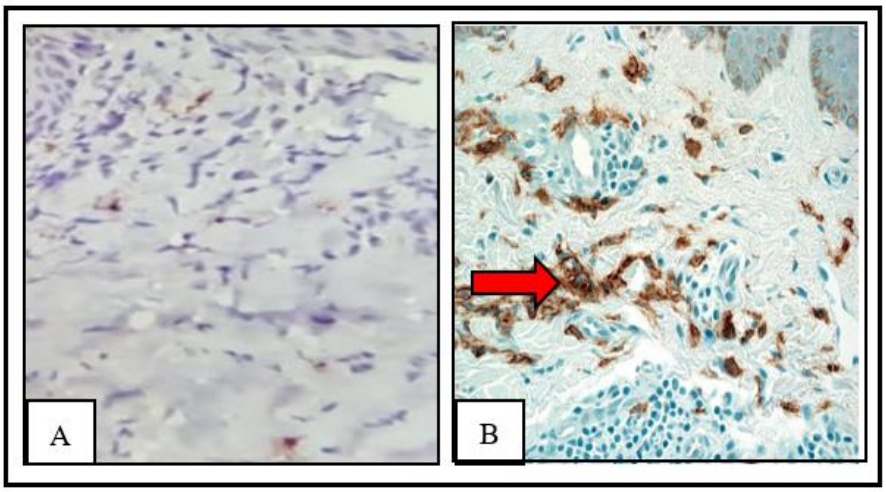


Figure 8

(A - B) Immunohistochemicals (IHC) S-100 in the dermis layer (A) In this patient appeared brown histiocytic cells (blue arrows) (B) In the literature appeared brown histiocytic cells (blue arrows)30 (magnification 100x) (C - D) Immunohistochemicals (IHC) CD-1a in the dermis layer (A) In this patient there is a picture of langerhans cells or Birbeck granules (green arrows) (B) In the literature there is a picture of langerhans cells or Birbeck granules (green arrows) (40x magnification) (Weedons's skin pathology, 2021).



Gambar 9

(a) Examination of patients with immunoohistochemicals (IHC) CD 117 in the dermis layer is not obtained mast cells (B) In literature with immunohisticimia (IHC) CD 117 in the dermis layer obtained a collection of brown mast cells (red arrows) (Weedons's skin pathology, 2021).

Conclusion

MS-type HSL patients have a prognosis of dubia ad night. Langerhans cell histiocytosis is a group of disorders characterized by the accumulation of langerhans cells that are accompanied by inflammation and cause tissue damage.

Enforcement of the diagnosis of MS-HSL is based on biopsy results, namely on microscopic preparations with the painting of Hematoxilin Eosin (HE) anterior trunkus skin tissue obtained the presence of small fragments of skin tissue, epidermis partially composed intact, dermis with powdered histiocyte cells, plasma cells, eosinophils, mast cell impressions and polymorphonononlear leukocytes and findings typical of biopsy results with

immunohistochemical staining with painting S-100 and CD1a i.e. the presence of a picture of langerhans cells or Birbeck granules.

The implementation of HSL depends on the criteria of HSL classification in patients. Patients get etopul® (etoposide) injection therapy 60 mg intravenous bolus / week and prednisone tablets 40 mg 3 divided doses, NaCl compress 0.9% for 10-15 minutes on thick krusta area, mometason cream for head, back and chest area as much as 2 times a day, gentamicin ointment oles 2 times daily on erosion area, On the 30th day of treatment the patient's condition has been improved.

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