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Case Report

62-Year-Old Woman with Severe Malnutrition and Toxic Epidermal Necrolysis

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Abstract

Malnutrition and skin problems are interrelated. Malnutrition may reduce the function of innate and adaptive immunity. There are immune cells in the skin that are crucial for host defense. A 62-year- old female patient was diagnosed with Toxic Epidermal Necrolysis (TEN) due to an unknown drug allergy and moderate to severe malnutrition. The patient had a history of inadequate intake for one year and has worsened during the last two weeks due to blistered and peeling skin, especially in the labium oris area after taking an unknown analgesic medication. Nutrition therapy with a target of 1900 kcal/day was administered and gradually increased to 2200 kcal/day through the enteral and parenteral route with a protein intake of 1.5 grams/kgIBW/day. Due to a history of food aversion to animal protein such as chicken, eggs, fish, cow's milk, and dairy products, soy-based polymeric formula and supplemental parenteral nutrition were administered to achieve nutrition requirements. Micronutrient supplementations including zinc, vitamin A, vitamin B complex, and vitamin C were given on day one of treatment. The patient experienced side effects due to systemic corticosteroids in the form of the moon face, severe muscle wasting, hyperglycemia, and hypertension. At the end of the treatment period, there were metabolic improvements such as wound healing without secondary skin infection and improvement of albumin serum from 2,3g/dL to 3,3g/dL.

Keywords: Aversion, Corticosteroid; Malnutrition; Toxic Epidermal Necrolysis

Abbreviations

IBW: Ideal Body Weight; CD: Cluster Differentiation; CRP: C-Reactive Protein; eGFR: estimated Glomerular Filtration Rate; ESPEN: European Society for Clinical Nutrition and Metabolism; GLIM: Global Leadership Initiative of Malnutrition; IL: Interleukin; MNA: Mini Nutritional Assessment; NK: Natural Killer; ONS: Oral Nutritional Supplementation; REE: Resting Energy Expenditure; SPN: Supplemental Parenteral Nutrition; TEN: Toxic Epidermal Necrolysis; TNF: Tumor Necrosis Factor

Introduction

Skin is the largest organ of the body, which is 15% of the total adult body weight. The skin is composed of three layers, namely the epidermis, dermis, and subcutaneous fat tissue. The epidermis is the outermost layer of the skin and is divided into the stratum corneum, stratum lucidum, stratum granulosum and stratum basale. The skin layer is supported by accretion of collagen tissue which acts as a physical, chemical and microbiological barrier to protect the host from external exposure [1,2].

Additionally, the skin contains immune cells that are important for host defense, homeostasis, and tissue maintenance. If there is external exposure, the immune cells present in the skin are essential not only for prevention of infection but also for tissue reconstruction. Damage to components of the skin's physical barrier can contribute to inflammatory conditions of the skin. The role of nutrition in inducing various skin disorders and skin diseases that cause nutrient deficiency has been widely reported [3].

Malnutrition and skin problems are interrelated. Malnutrition will reduce innate and adaptive immunity, thereby increasing the risk of infection. The infection will cause metabolic stress, weight loss, and sarcopenia, thereby weakening immune function and nutritional status. Likewise, Toxic Epidermal Necroysis (TEN) requires adequate nutrition for wound healing and nucleotide synthesis. Various literatures show that nucleotide synthesis is associated with increased immunity and intestinal tissue. The presence of nutritional deficiencies can interfere with the wound healing process. Malnutrition will reduce the strength of the wound and increase the risk of infection. This case report will discuss severe skin disease, namely TEN and risk factors related to nutrition and nutritional therapy [1,4,5].

Case Report

A 62-year-old female patient was diagnosed with TEN due to unidentifiable drug allergy and moderate to severe malnutrition. The diagnosis of TEN in patients was obtained from the history that the patient experienced blisters all over the body after taking anti-pain medication even though anti-pain drugs are known to rarely cause SJS (Steven Johnson's Syndrome) or TEN. Anthropometric examination of the patient showed that the patient's weight based on upper arm circumference was 64 kg, height 160 cm, body mass index (BMI) 25 kg/m^2, muscle wasting (+2/+2), loss of subcutaneous fat (+2/+ 2), minimally edema of the lower extremities. Estimates of body weight based on upper arm circumference are calculated using the formula, then BMI measurements are obtained from body weight in kg divided by the square of body height in meters. The decrease in muscle mass and subcutaneous fat in patients is moderate, so it is likely that the malnutrition experienced by the patient has been going on for quite a long time, even though the patient's BMI is still classified as overweight. Examination of hand grip strength could not be carried out because of pain in the skin lesions on the hands. Laboratory results showed hemoglobin levels of 10g/dL, leukocytes 8.4 x 10^3/uL, urea 31 mg/dL, creatinine 0.8 mg/dL, and eGFR 92.95 mL/minute/1.73 m^2, eosinophil count 0%, 1% basophils, 0% rods, 65% segments, 21% lymphocytes, 10% monocytes, quantitative CRP 6.59 mg/dL, and albumin level 2.3 g/dL. Chest X-ray examination shows bronchopneumonia.

The patient has a history of this disease and has been hospitalized up to four times a year at the Rembang District Hospital but has not been routinely monitored properly. The patient has a history of obesity since he was young and has an aversion to animal protein such as chicken, eggs, fish, cow's milk and dairy products. The patient has received nutritional therapy since the first day of treatment. When entering the hospital, patients consulted the ophthalmologist, ENT, and internal medicine specialist. The patient received corticosteroid injections for 23 days with the dose reduced slowly by the doctor in charge of the patient, a specialist in dermatovenerology. During treatment, the patient receives blood sugar monitoring to monitor side effects of the corticosteroid injections given.

Nutritional therapy is given with an energy target of 35 kcal/kgIBW/day and 1.5 gP/kgIBW/day protein in the form of sweet coconut rice porridge and Oral Nutritional Supplementation (ONS) because the patient complains of pain in the lip area due to peeling skin. Giving ONS in the form of liquid food through a sonde for Kariadi Hospital's formula containing skim milk, sugar, sweet oranges, cornstarch, corn oil, eggs and water as well as a soy-based formula. Patients were also given supplementation for wound healing in the form of 100,000 IU vitamin A capsule given as a single dose, 300 mg/8 hours of vitamin C tablets, 1 tablet/8 hours of vitamin B complex tablets, and 20 mg/12 hours of zinc tablets given during treatment at the hospital until the patient goes home. [2] Notes on the progress of nutritional therapy given to patients can be seen in table 1.

Treatment Day	Nutrition Therapy	Supplementation
Day 1	35 kcal/1,5 gP/kgIBW/day : sweet coconut rice porridge + polymeric formula	vit. A, vit C, vit B complex, and zinc
Day 2	35 kcal/1,5 gP/kgIBW/day : rice porridge with chopped side dishes + soy-based polymeric formula + SPN	vit C, vit B complex, and zinc
Day 9	35 kcal/1,8 gP/kgIBW/day : rice porridge with chopped side dishes + soy-based polymeric formula + SPN	vit C, vit B complex, and zinc
Day 11	40 kcal/1,8 gP/kgIBW/ day: rice porridge with chopped side dishes + soy-based polymeric formula + SPN	vit C, vit B complex, and zinc
Day 21	40 kcal/1,8 gP/kgIBW/day: steamed rice with chopped side dishes + soy-based polymeric formula + SPN	vit C, vit B complex, and zinc

Table 1: Follow up on patient nutrition therapy.

Good outcomes are characterized by wound healing, increased functional capacity, optimal nutritional status, and increased quality of life. The patient demonstrated wound healing during hospitalization and did not develop secondary infectious complications (Figures 1-4). The patient also experienced an increase in serum albumin from 2.3 g/dL to 3.3 g/dL.

Discussion

Malnutrition can be defined as a condition resulting from a lack of intake or absorption of nutrients which causes a change in body composition (decreased tissue mass) and body cell mass which causes a decrease in physical and mental function and interferes with the clinical outcome of the disease. In brief, according to the European Society for Clinical Nutrition and Metabolism (ESPEN) prior to a diagnosis of malnutrition the criteria of "at risk of malnutrition" with a validated nutrition risk screening tool must be met. Patients were consulted to the clinical nutrition department from the first day of hospitalization. Nutrition screening in this patient used a Mini Nutritional Assessment (MNA) and it was concluded that this patient was at risk of malnutrition and in the MNA assess-

Figure 1: 1st day treatment.

Figure 2: 5th day treatment.

Figure 3: 17th day treatment.

Figure 4: 23rd day treatment.

ment section a score of severe malnutrition was obtained. This patient may have been malnourished for the past year because moderate to severe loss muscle wasting and loss of subcutaneous fat were found on physical examination related to nutrition. examination related to nutrition [3].

Overweight and/or obesity nutritional status affects wound healing through several mechanisms. Excessive adipose tissue alters the cellular composition and structure of adipose tissue and alters the physiology of the skin and subcutaneous tissue. Obesity induces adipocyte hypertrophy and hyperplasia leading to metabolic dysfunction. Following metabolic dysfunction, inflammatory mediators begin to invade adipose tissue, causing chronic, low-grade inflammatory processes associated with obesity. The phenotypic switch from protective M2 macrophages to proinflammatory M1 macrophages exacerbates this problem. Obese adipose tissue secretes angiogenic inhibitors and fibrotic mediators [4].

Extracellular matrix remodeling can further inhibit the process of angiogenesis by creating a more rigid environment and preventing migration of cells and blood vessels. Without an adequate vascular supply to oxygenate the area, relative hypoxia ensues. Hypoxia induced by capillary damage in the wound and relative hypoxia in obese individuals likely contribute to higher wound infection rates in obese patients due to lower oxygen tension from decreased perfusion and impaired immune system function. In addition, hypoxic wounds impair mature collagen synthesis, leading to weaker tissue and deficiencies in the overall healing process. Thus, microvascular abnormalities as a result of excessive adiposity contribute to obesity-associated microangiopathy. Vascular insufficiency and changes in the population of immune mediators present can prolong the inflammatory stage of wound healing, as well as make obese individuals more susceptible to infection. Wound healing is also delayed due to deficiency of macronutrients and micronutrients in obese individuals. Without the proper cofactors and enzymes, the wound healing process and wound integrity can be compromised [4].

Malnutrition is a complex mechanism. The complexity of the interaction between nutrition and immunology is vast. An individual's overall nutritional status, nutritional state, and nutritional intake patterns (consisting of macronutrients, micronutrients and non-nutritional bioactive compounds) influence the function of the immune system. These impacts may occur at the level of physical barriers (eg, skin, lung epithelium, intestinal mucous membranes), microbiome, innate immune system (eg, macrophages, dendritic cells, and NK cell function and polarization) and the adaptive immune system (eg, T and B cell function). In contrast, the immune system influences metabolism and nutrient requirements and influences physiological responses to nutritional status. The etiology-based classification of malnutrition diagnoses is supported by the Global Leadership Initiative of Malnutrition (GLIM) as previously suggested by the International Consensus Guideline Committee. Table 2 shows the diagnoses of malnutrition based on the ESPEN GLIM consensus. According to the GLIM criteria the patient was diagnosed as moderately malnourished because there was one phenotypic criteria in the form of a moderate muscle wasting and etiological criteria in the form of an 8.57% weight loss in the past year and the patient looked thinner in the last two weeks [5,6].

Phenotypic Criterion	GLIM criteria for moderate malnutrition (requires 1 phenotypic criterion that meets these criteria)	GLIM criteria for severe malnutrition (requires 1 phenotypic criterion that meets these criteria)	Found in patients
Weight loss (%)	5-10% within the last 6 months or 10-20% more than 6 months (requires 1 phenotypic criterion that meets these criteria)	>10% in the last 6 months, or >20% more than 6 months	8.57% in the last 1 year. The patient looks thinner in the last 2 weeks.
Body Mass Index (kg/m^2)	<20 if <70 years, <22 if ≥ 70 years	<18,5 if <70 years, <20 if ≥ 70 years	BMI 25 kg/m^2
Decreased muscle mass	Mild to moderate deficit (based on validated assessment methods)	Severe deficit (based on validated assessment methods)	Moderate deficit based on anthropometric measurements

Table 2: Malnutrition criteria based on GLIM, 2019 [6].

The prevalence of malnutrition among hospitalized older adults varies widely depending on the population studied and the criteria used for diagnosis. Nearly 55% of elderly patients who are hospitalized are malnourished or malnourished upon admission to hospital. Elderly is an elderly person, namely someone aged 60 years and over according to Permenkes No. 79/2014. According to ESPEN, geriatric patients are not defined specifically based on age, but are characterized by a high degree of frailty and multiple active diseases which are common in the age group over 80 years. Diseases that are often experienced by geriatric patients are known as Geriatric Giants, including cerebral syndrome, confusion, autonomic disorders, incontinence, falls, bone disorders and fractures, and decubitus. The clinical disturbances experienced by patients can cover a wide spectrum, including apraxia, gait, dementia, and incontinence. Apart from Geriatric Giants, the term geriatric syndrome is also known, which helps solve problems in geriatric patients. This problem-solving method is known as the 14 I (immobility, instability, incontinence, intellectual impairment, infection, impairment of vision and hearing, irritable colon, isolation, inanition, impecunity, iatrogenesis, insomnia, immune deficiency, and impotence) [7,8].

The patient is elderly and has a geriatric syndrome; There are 6Is experienced by patients, namely immobility, instability, infection, inanition, impeccability, and immune deficiency. Inanition or malnutrition which is included in the 6I experienced by patients then triggers the appearance of TEN or skin disorders experienced by patients requiring hospitalization. Availability of complement components and impaired phagocytic function during malnutrition will directly affect pathogen elimination. This occurs either because the complement system itself can destroy bacteria or viruses or because complement receptors present on the surface of phagocytes mediate pathogen capture. Complement levels are much lower, especially C3 which is the main opsonic component. In addition, the ability of phagocytes to engulf and kill pathogens is also reduced during malnutrition [9].

The effect of malnutrition on nutritional status can be divided into four major patterns, namely anorexia, increased metabolic rate, and specific nutrient needs. Anorexia is common in infectious processes and is a major contributor to wasting in chronic infections. Pro-inflammatory cytokines themselves play a role through neuropeptides such as NPY to suppress appetite centers in the hypothalamus. REE usually increases in acute infectious conditions, mostly due to fever. However, the increase in energy expenditure is balanced by a decrease in energy requirements due to decreased activity. Therefore, total energy expenditure does not increase in sick patients who are inactive but energy requirements are often overestimated in that condition. Although negative energy balance is common, the most common cause is a decrease in intake so as not to increase expenditure [8].

Severe malnutrition is associated with atrophy of the primary lymphoid organs, namely the bone marrow and thymus which then lead to disturbances in the regulation of T cells and B cells. The direct result of this atrophy is leukopenia, decreased CD4/CD8 ratio, and increased number of immature T cells in the periphery. Alterations in the morphology of thymic epithelial cells associated with decreased thymic hormone production have also been described during conditions of malnutrition. These changes appear to be related to a hormonal imbalance involving a decrease in leptin and a consequent increase in serum glucocorticoid hormone levels. A series of studies have shown that the biological functions of various cell types (B lymphocytes, macrophages, and Kupffer cells) are markedly decreased during conditions of malnutrition. The immune response of the epithelial barrier is also greatly affected by malnutrition. These changes are primarily characterized by changes in intestinal mucosal architecture including flattening of the hypotrophic microvilli, dysbiosis, decreased lymphocyte count in Peyer's patches, and decreased secretion of immunoglobulin A [9].

There are several mechanisms by which malnutrition increases vulnerability against infection. Layer integrity barriers such as skin and mucosa acts as the first line of defense. Fighting infection is impaired when the condition is presents malnutrition. Cellular immune function and humoral is also very disturbed at malnourished individuals. As a result, Malnourished patients experience episodes of infection which are more frequent and more severe. this effect more noticeable at the extreme ages. On perinatal period, when the immune system, especially the thymus is developing, Immunity can be severely compromised as a result malnutrition. Elderly individuals who already have associated immune dysfunction. Age (immunosensitivity) is more at risk great for infection and malnutrition. Malnutrition can alter disease relatively mild to be a condition life threatening. Interactions between infections and malnutrition can be seen in figure 5. [10,11].

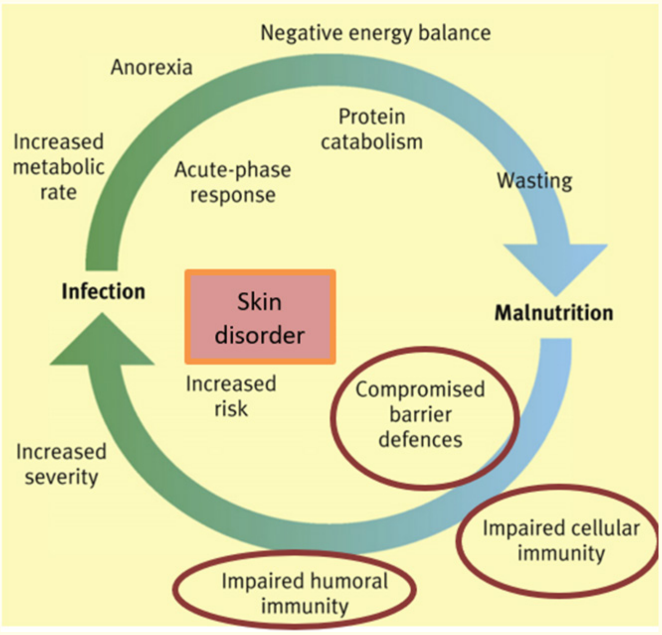

Figure 5: Interaksi Infeksi dan Malnutrisi, dimodifikasi dari Derek Macallan, 2009 [11].

Research also shows that malnutrition has a negative impact on the wound healing process. Malnutrition prolongs the inflammatory phase by reducing fibroblast proliferation and collagen formation as well as reducing tensile strength and angiogenesis. It can also place the patient at risk of infection by decreasing T-cell function, phagocytic activity, and complement and antibody levels.

This change in immune function can lead to an increase in wound complications such as delays in wound healing. However, the patient was not subjected to immunoserological examination to assess decreased T cell function [4,12].

Corticosteroids are one of the therapies that are often given to skin disorders. Corticosteroids have many benefits in treating inflammation and autoimmune disease because of the significant anti-inflammatory and immunosuppressive effects of corticosteroids. Corticosteroids are used in pharmacological doses to suppress allergic or inflammatory responses but these agents can cause many side effects associated with excessive glucocorticoid activity. Long-term use (>2 weeks) results in suppression of the hypothalamus-pituitary-adrenal axis, requiring a dose reduction. The dosing strategy for systemic corticosteroids is designed to minimize the risk of suppression of the hypothalamic-pituitary-adrenal axis. In addition, these agents influence energy, protein, and lipid metabolism, which results in gluconeogenesis, protein catabolism, and mobilization of fatty acids along with several other effects. The long-term consequences of using pharmacological corticosteroid therapy are severe and predictable, including problems associated with suppression of the hypothalamic-pituitary-adrenal axis, osteoporosis, immunosuppression, muscle wasting, and changes in physical appearance [13].

This patient received corticosteroid injection therapy from the first day of hospitalization (125 mg every 12 hours) until discharge from the hospital (for 23 days) with the dose reduced gradually. The side effects of systemic corticosteroids in this patient were clearly seen in the form of a moon face, hyperglycemia, and hypertension. The side effects of systemic corticosteroids related to the metabolism of macronutrients and micronutrients are also clearly visible in the form of increasing muscle wasting experienced by patients even though the nutritional intake given has reached the target.

Conclusion

Malnutrition and TEN have an interrelated relationship. Severe malnutrition can cause innate and adaptive immune system disorders, where these immune disorders can ultimately worsen wound healing in TEN. Obesity nutritional status can also lead to impaired wound healing due to low-grade inflammation that occurs in obesity. Meanwhile, TEN can also exacerbate malnutrition due to an increase in proinflammatory cytokines and chemokines. This increase in pro-inflammatory cytokines can cause an increase in resting energy expenditure (REE) and trigger proteolysis and lipolysis which, if not balanced with adequate intake, will lead to malnutrition. Malnutrition and infection work in an unfortunate reciprocal synergism. Malnutrition predisposes to infection and increases the severity and mortality of infection. Infection reduces nutrient intake, impairs substrate utilization, and increases tissue damage. This also contributes to the link between malnutrition and impaired wound healing. Corticosteroids are one of the therapeutic options given to skin disorders but the long-term consequences of the pharmacological use of corticosteroid therapy are quite severe. Therefore, the use of systemic corticosteroids must pay attention to whether the benefits outweigh the disadvantages. Provision of adequate nutrition therapy will synergize with medical therapy and medical rehabilitation so as to produce better outcomes. Good outcomes are characterized by wound healing, increased functional capacity, optimal nutritional status, and increased quality of life [2,3,13].

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Conflict of Interest

The authors declare that they have no conflict of interest.

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