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EXFOLIATIVE DERMATITIS SECONDARY TO THYMOMA: A RARE ASSOCIATION

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ABSTRACT

Exfoliative dermatitis (ED), also referred to as erythroderma, is a scaling erythematous dermatitis involving 90% or more of the cutaneous surface. In ED the rate of epidermal turnover, the number of germinative cells, and their absolute mitotic rate are increased. ED is most commonly idiopathic, but may also be secondary to pre-existing dermatoses; drug-eruptions or atopic dermatitis, drug reactions and malignancies .Chinese herbal drugs have also been implicated. This is a case report of a 36year old Chinese female with Exfoliative dermatitis secondary to recurring thymoma stage IIIB with background history of Myasthenia gravis. The case highlights the rare association of thymic tumours with Exfoliative dermatitis and also reminds clinicians to aggressively evaluate patients for possible malignancies in cases of unexplained causes of exfoliative dermatitis.

KEYWORDS: exfoliative dermatitis, erythroderma, thymoma, myasthenia gravis.

KEY MESSAGES: exfoliative dermatitis due to thymoma is rare and its prognosis is dependent on the stage of the thymic tumour and other commodity conditions. This is the first reported case of exfoliative dermatitis in Chinese (Han) national.

INTRODUCTION

Exfoliative dermatitis (ED), also referred to as erythroderma, is a scaling erythematous dermatitis involving 90% or more of the cutaneous surface. In ED the rate of epidermal turnover, the number of germinative cells, and their absolute mitotic rate are increased.

ED is most commonly idiopathic[1], but may also be secondary to pre-existing dermatoses like lichen planus[2], psoriasis, drug-eruptions or atopic dermatitis[3], drug reactions like isoniazid(anti tubercular)[4], Chlorambucil-associated allergic skin reactions[5], imatinib[6], anti- convulsants like Phenobarbital[7] and malignancies like lymphoma[8], leukaemia[9], other malignancies(renal cell carcinoma[10] and Chinese herbal drugs have also been implicated.

The pathophysiological mechanisms involved in the clinical manifestations of exfoliative dermatitis depend on the condition's cause. In general, however, the regeneration rate of the epidermal cells of these patients has been found to be significantly increased. Cells found in the germinative layer, the deepest epidermal skin layer from which new tissue is formed, are considerably more in number than in healthy individuals. In addition, the process of cell apoptosis and replacement requires less time to complete. As a result of these abnormalities, the epidermal layer is frequently replaced, which results in the manifestation of the exfoliating symptom.

Complex interactions between interleukins (IL-1, IL-2,IL-8), the tumour necrosis factor (TNF) and the intercellular adhesion molecule 1 (ICAM-1) are believed to play an important pathogenetic role in this condition . A further notable difference between the characteristics of a normal epidermal turnover procedure and that of exfoliative dermatitis is that in healthy individuals, the exfoliated skin contains no proteins, amino acids or nucleic acids; in the case of exfoliative dermatitis, these substances are disposed off in great quantities with exfoliation.[11] [12] This explains the high requirement of proteins in their diets.

Thymoma, a thymus tumour; originates within the epithelial cells of the thymus, a lymphoid organ located in the anterior mediastinum. This organ is located behind the sternum in front of the great vessels; it reaches its maximum weight at puberty and undergoes involution thereafter. In early life, the thymus is responsible for the development and maturation of cell-mediated immunologic functions. The thymus is composed

predominantly of epithelial cells and lymphocytes. Precursor cells migrate to the thymus and differentiate into lymphocytes. Most of these lymphocytes are destroyed, with the remainder of these cells migrating to tissues to become T cells.

Blalock et al first established the relation between myasthenia gravis (MG) and thymomas incidentally in 1939, when reported the first excision of a thymic cyst in a 19-year-old girl with MG.[13] This patient achieved long-term remission; therefore, thymectomy became the definitive therapy for treatment of generalized MG.

No clear histologic distinction between benign and malignant thymomas exists. The propensity of a thymoma to be malignant is determined by the invasiveness of the thymoma. Malignant thymomas can invade the vasculature, lymphatics, and adjacent structures within the mediastinum. The 15-year survival rate is 12.5% for a person with an invasive thymoma and 47% for a person with a non-invasive thymoma. In patients with thymoma,death usually occurs from cardiac tamponade or other cardiorespiratory complications.[14]

In this review we shall discuss a rare association of exfoliative dermatitis in a 36year old Chinese lady secondary to Thymoma. There are no case reports of ED due thymoma reported in Chinese nationals. However, there are at least four case of Graft Versus Host Disease(GVHD)-like erythroderma associated with Thymoma.[15]–[18] Animal cases have been reported, ED in cats due to thymoma.[19]

CASE HISTORY

She was 36years old, Para one, married, and Han by ethnicity. Referred via two local hospitals being managed for suspected Drug induced dermatitis for at least over a month in the background of myasthenia gravis for over 4years and being evaluated for recurring thymus tumour stage IIIB of 2years on a cocktail of drugs; methylprednisinolone, Tarclolimus, pyridostigmine, omeprazole and antihistamines,neuquinon(Co-Enzyme Q10).

The patient had being in slightly fair state of health for the past 4years until about 2weeks prior presenting to the hospital with history of worsening itchy skin rash. She gave history of using Chinese herbal medicines, for rubbing on the body (Chinese method of healing) and calamine lotion with little or no improvement.

At the local hospital, she gave a 2weeks history of worsening itchy, dry skin which was said to be painful in the last 2days prior visit to our hospital. This episode was associated with severe muscle weakness, anorexia, reduced urine output, productive cough not suggestive of tuberculosis. Also gives history of vertigo, headache - dull ache in nature. However, she denied history of nausea, vomiting, neck ache, fever or any ear discharge.

She denies any history of tuberculosis, HIV/AIDS, convulsive disorder, hepatitis B, syphilis, hypertension, diabetes melitus or any other skin disorders. She has a history of caesarean section 15years ago, thymectomy 5years ago (thymus tumour reported to have recurred 3years ago, staged as IIIB.).

She has no known drug or food allergies and does not drink alcohol or smoke cigarette.

On examination she was ill looking, lethargic, not in obvious respiratory distress. She was oriented in Time, Place and Persons. Her vitals: Temp 38°C, pulse 80/min (fluctuating max 150/min) BP 86/57mmhg (MAP=67mmhg), RR=19min.Her pupils where equal, reacting to light. She was not pale, jaundiced or any lymphadenopathy. Kerning sign was negative. Oral cavity reviewed first degree (1°) hypertrophic tonsils with hyperaemic pharynx.

She had erythematosus macules over the forehead, becoming oedematous over the cheeks .The lesions on the trunk and both upper and lower limbs were maculopapules over an erythematous surface. The lesions show a centripetal pattern with excoriation especially on trunk. The dermatitis was worsening with time, associated fissuring and occasional crustation especially on flexure regions.

She has no hepatosplenomegaly or any bone tenderness. The rest of the examination was unremarkable.

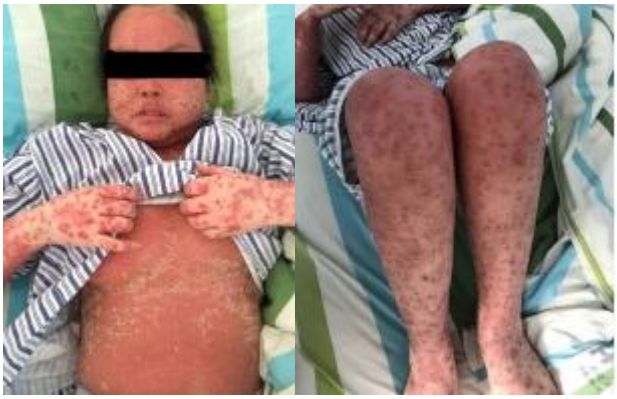

Figure 1(a-b) erythroderma with macular lesions, xerosis, crustation and excoriation (picture courtesy of Dr Jiang Si, Zhongnan Hospital of Wuhan University.).

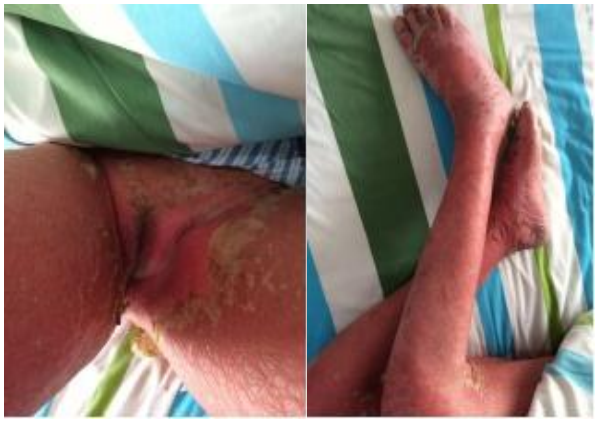

Figure 2(a-b) ED showing severe exfoliation on the intertriginous areas with associated fissuring. (Picture courtesy of Dr Jiang Si, Zhongnan Hospital of Wuhan University.)

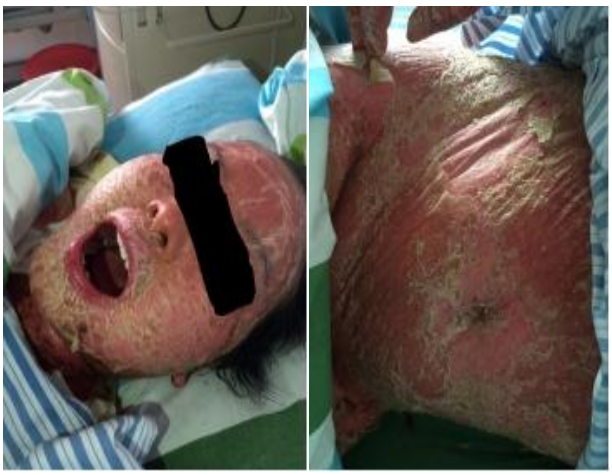

Figure 3 (a,b) ED after weeks of admission showing worsening erythroderma; icthioyosis like cutaneous lesions, increased fissuring in flexure areas.(picture courtesy of Dr Jiang Si, Zhongnan Hospital of Wuhan University.)

MANAGEMENT

A multidisplinary approach was used in management of our patient according to the treatment protocol of the institution. Investigations done; of note was the complete blood count which was suggestive of an acute infection with leukocytosis of 16.6*10^9/L neutrophilic dominance of 92%, lymphocyte 4.7%. However, there was no eosinophilia and other parameters were within normal range. Skin swab culture was positive for fungus. The autoimmune disease screen gave positive results for Antinuclear antibodies (ANA), Smith`s antibodies(Sm), Anti dsDNA antibodies, Anti-histone antibodies and Anti-Scl 70 antibodies. The positive autoimmune results points to the co-morbidly condition myasthenia gravis the patient had. On the blood chemistry, of not was hypoproteinemia and hypoproteinemia of 48g/L and 30g/L respectively. Immunoglobulins were also reduced, 17.3 µg/L. Creatinine Kinase was increased due to disease processes (myasthenia gravis and erythroderma). Liver enzymes (ALT, AST and LDH which were 66IU/L, 64IU/L raised to 319IU/L respectively) had a slight insignificant raise. Direct and total bilirubin was normal. There was an expected rise in C-Reactive Protein (CRP) of 142.77. The electrolyte panel (potassium, calcium, sodium, uric acid), TORCH and Viral Screen were unremarkable. Alpha feto protein(AFP) done was 125.7IU/L.

The skin biopsy from the dorsum of foot showed; epithelial hyperplasia with infiltration by chronic inflammatory cells.

Computerized tomography(CT) scan of chest revealed right lower lobe infiltrates suggestive of an infective process, mediasternal lymphadenopathy, bilateral pleural thickening.

Exfoliative Dermatitis from whatever cause is a potentially life-threatening condition with risks of septicemic infections, hypoalbuminemia, hyperpyrexia and hypernatremic dehydration largely due to massive damage to the skin. Therefore, careful management of ED would include monitoring of vital signs and electrolyte levels, adequate oral or parenteral fluid intake, prevention and treatment of infection, correction of caloric and protein balance, topical application of emollients or antifungals, wet dressings, or steroids. Recognition and proper diagnosis by a dermatologist is necessary to prevent treating the condition wrongly with topical corticosteroids.[20]

The patient was to be nursed in High dependency Unit but the family members declined the offer. However, patient was kept warm daily. The patient was on continuous ECG tracing machine, temperature, oxygen saturation et cetra monitoring especially during the myasthenia gravis crisis. The fluid and electrolyte correction and balance was archived using intravenous solutions and in correlation with the blood gas analysis. She had nutritional support, a high protein diet in addition to parenteral feeds. Our client was on a cocktail of medications for recommended duration: Immunoglobulins intravenously, Anti inflammatory-Methlyprednisolone, intravenous calcium gluconate in 5% Dextrose Normal Saline, Proton pump inhibitor-omeprazole ,intravenous Vitamin C and septic cover-antibiotic as commanded by culture results, antifungal and anti viral prophylactic cover. Psycho-social support to both patient and family members was offered. The clinicians discussed with next of kin on diagnosis and prognosis of patient.

Unfortunately the patient demised due to over whelming Multiple Organ Damage secondary to severe sepsis and advance primary disease condition.

DISCUSSION

Exfoliative dermatitis(ED) is clinically diagnosed. What is of vital importance is the underlying primary causative condition? The delay in diagnosis of ED was partly due

to the co-morbid conditions our patient had. She was treated for initially as a drug induced dermatitis then acute allergic urticarial(allergen was suspected drug).After a viral screaen,viral exanthema was entertained but the positive autoimmune screen and increasing levels creatinine kinase made Lupus erythromatosus entertained with differentials of dermatomyositis, complex connective tissue disease. But Myasthenia gravis crisis explains the positive autoimmune screen results. After a concerted effort, advanced thymoma stage IIIB was the attributing factor of the exfoliative dermatitis. The condition was not improving despite patient being on the standard treatment for ED. Patient had spiking temperatures despite being on broad antibiotic; fear of superbug infection was entertained.

This case highlights the important clinical features of exfoliative dermatitis and emphasizes those dermatoses with unclear aetiologies warrant thorough evaluation with an age-appropriate workup for malignancies. It must be emphasized that a high index of suspicion for malignancy in patients with dermatoses of unclear aetiologies may result in early diagnosis and appropriate treatment. In this case thymoma induced exfoliative dermatitis.[12] [21] This is a rare association, which has never been documented among Chinese nationals but Graft Versus Host Disease(GVHD)-like erythroderma associated with thymoma have been reported in different ethnic groups.[15]–[18] However, GVHD-like erythroderma could not be entertained as our patient had no risk factors which could attribute them to get GVHD-like erythroderma.Reports of thymoma in animal study had been documented.[19]

Even though exfoliative dermatitis is a complex disorder involving many factors, the underlying disease is usually the key determinant of the course and prognosis.[22] Drug-induced exfoliative dermatitis is usually short-lived once the inciting medication is withdrawn and appropriate therapy is administered. Patients with underlying skin disorders may respond much more slowly to therapy, but clearing almost always occurs eventually. The clinical course of patients with malignancies depends on the type of malignancy and the response to appropriate therapy. Patients who have exfoliative dermatitis of unknown cause tend to have an unpredictable course, usually replete with multiple remissions and exacerbations.[11][23]

Bao et al demonstrated that fever is generally considered a bad prognostic factor as was with our patient.[24] Children younger than 3 years old, with exfoliative dermatitis, hypotension, sickly appearance and a high creatinine value run a higher risk of developing toxic shock syndrome. Mortality rates fluctuate between 20 and 40%. Wilson DC et al showed that in 1/5 of the instances, death occurs from factors irrelevant to exfoliative dermatitis.[12]

The prognosis is worse for patients with symptomatic thymomas because these patients are more likely to have a malignant thymoma, like in the case with our patient(evidenced by relapse of malignancy). The single most important factor predicting the outcome of patients with thymomas is evidence of invasion. Histologic characteristics, such as microscopic capsular invasion should be assessed. The surgeon should perform a gross inspection. Cellular characteristics are inconsequential because they have no impact on patient treatment. Because of the well-documented propensity for late recurrences, long-term survival should be considered in terms of a 10-year follow-up after treatment of the thymoma. A study conducted by the Memorial Sloan-Kettering Cancer Centre reported 5-year and 10-year survival rates to corresponding stages of thymomas. For stage I and II the 5 and 10 year survival was found to be at 90% and 80% respectively for both stages and in stage III ,5 and 10year survival rate was found at 60% and 30% respectively while for stage IV at less than 25% for 5year survival.[11] Thymomas are associated with the development of second malignancies. However,our client did not have any secondary malignancies.

The clinical course of Myasthenia Gravis (MG) included remission, relapse, exacerbation and death. About 38% MG patients experienced remission.[25] One study demonstrated that early thymectomy and administration of prednisolone were more frequently seen in the complete remission cases than in the relapsed ocular myasthenia gravis (OMG) patients.[26]

As they say that the skin is the window to the possibility of knowing or suspecting some systemic condition(s). Exfoliative dermatitis as such can give clinicians the hint of a possibility of a systemic condition or malignancy thus referred to as a" friend" but at the same time it can expose the patient to a lot of complications thus referred as a "foe." Severe complications that can manifest secondarily to exfoliative dermatitis; erythroderma include infections due to loss of the protective epidermal layer, electrolyte imbalance and cardiac arrest[9], with patients largely succumbing to cardiac arrest, pneumonia or septic shock.

Initial management of erythroderma focuses on correcting fluid and electrolyte imbalances. Oral antihistamines might relieve pruritus. Topical treatments include oatmeal baths followed by application of bland emollients and low-potency corticosteroids. In suspected drug-induced cases, discontinuing medication is mandatory. Hospitalization should be considered for patients with high output cardiac failure and systemic disease. Secondary management focuses on identifying and treating the underlying cause. Acitretin, isotretinoin, cyclosporine, systemic corticosteroids, or other immunosuppressives can be used, depending on the underlying cause.[8]

In conclusion, any and every case of exfoliative dermatitis should be adequately and appropriately evaluated. I wish to propose that chronic dermatoses of unexplained etiology, workup for malignancies should be initiated for all patients. Thymoma in humans also can cause or is associated with exfoliative dermatitis.

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CONFLICT OF INTEREST

Nil.

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