The US food and drug administration has implemented new regulations to increase the number of drugs available for pediatric use. In Europe, similar changes are under discussion, currently only with very limited success.

Conclusion
Prescribing an unlicensed or 'off-label' medicine is not illegal, but it is a risk management that needs to be addressed. So that the recognition of the importance of studying drugs for use in children and the establishment of various initiatives is to be applauded.

Acknowledgement
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Netherton’s Syndrome: A Case Report

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Abstract
We report a case of a 12.5 years old male patient who presented to the dermatology clinic complaining of pruritic scaly dry skin and sparse brittle hair. Clinical and laboratory assessment revealed ichthyosis linearis circumflexa, trichorrhexis and atopy. These findings fit the diagnosis of Netherton's syndrome. Family history is also positive for the same disease.

Netherton’s Syndrome (NS) is a rare autosomal recessive disorder, first described by Netherton in 1958 in a girl with erythematous scaly dermatitis who had 'bamboo-like nodes' in her sparse fragile hairs. The classical triad of clinical features includes ichthyosis, hair shaft abnormalities and atopic diathesis. The disease has an estimated incidence of 1 in 100,000. Only three cases have been published from the Arab World, and to the best of our knowledge, our case is the first to be published from Jordan.

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Clinical Examination: On presentation, the patient was consumed with itching. He had decreased growth parameters: a weight of 29 kg and a height of 138 cm, both falling below the 5th percentile on growth chart. He also had short, lusterless, sparse, beaded and easily broken hair with sparse eyebrows and eye lashes as well, figure 2. Seborrheic–like scales and erythema of the face were also noted. His body was covered by polycyclic, serpiginous, erythematous plaques with double-edged scales along the margin (which is called ichthyosis linearis circumflexa, ILC), figure 3a. Flexural lichenification was also evident. Histological examination of lesional skin showed features typical of ILC: (parakeratosis, marked psoriasiform acanthosis and papillomatosis of the epidermis, with perivascular mixed cell infiltrates in the papillary dermis), figure 3b.

Laboratory Findings: Light microscopy of scalp and eyebrow hair showed trichorrhexis invaginata and pili torti, figure 4 (a and b).

Complete blood count showed a White Blood Cell count (WBC) of $9.1 \times 10^9$ /L, with moderate eosinophilia at 7.3% of WBC. Normal eosinophil count is up to 4%.

His hemoglobin level was 12.9 g/dl, with normocytic normochromic red blood cells.

The erythrocyte sedimentation rate was 10 ml in the first hour.

Fasting blood sugar, liver enzymes, blood urea nitrogen, serum creatinine and urinalysis were all normal. Serum Zinc level was 11 micromol/L (normal: 7-18 micromol/L). Arterial blood gas analysis was within normal for all parameters and blood ammonia level was 0.6 micrograms/mL (normal level is up to 0.8 micrograms/mL).

Immunoglobulins (Ig) serum levels showed increase in IgE level (IgE: 530 IU/ml, normal level: below 100 IU/ml). Other Ig levels were all within normal range: IgG: 1247 mg/L (700-1600), IgA: 139.6 mg/L (70-400), IgM 75.66 mg/L (40-230).

RAST (Radio-Allergosorbent-Test) revealed that the patient is allergic to many substances, including: grass, brich, ragweed, dermatophagoid pt., dermatophagoid farina and plantain. He was also shown to be sensitive to olive, wheat, rice and rye as well as hazelnut, almonds, tomato, carrots and potatoes.

Urine chromatography for amino acids and other organic acids was negative.

Management: The patient has been started on regular antihistamines (hydroxyzine hydrochloride and loratadine), emollients and keratolytics (5% lactic acid). Mild topical steroids were prescribed to be used intermittently for facial lesions. Most recently, he was started on topical pimecrolimus, which is showing promising symptomatic relief.
Discussion

Netherton’s Syndrome is a rare autosomal recessive disorder with variable expression, mainly affecting females. The gene involved in the pathogenesis of NS (SPINK5 gene) has been mapped by linkage analysis and homozygosity, gene locus is on chromosome 5q32. This gene encodes serine protease inhibitor called LEKTI (Lympho-Epithelial-Kazal-Type Inhibitor), which is expressed in epithelial and lymphoid tissues. Different mutations have been described that lead to impaired proteolysis and so keratinocyte cornification and differentiation resulting in skin barrier defect. LEKTI might also be directly involved in the specific and innate immune system. The availability of molecular data opened the door for molecular diagnosis of NS and successful prenatal testing was achieved.

Patients with NS, like our patient, usually present with generalized erythroderma shortly after birth. The affected neonates are at risk of hypernatremic dehydration, temperature instability and sepsis. Another reported complication during the neonatal period is dermopathic enteropathy that manifests as diarrhea and failure to thrive even with appropriate dietary supplements. Jejunal villous atrophy was reported in one case out of three cases in one study which resolved spontaneously at the age of 10 months. At the neonatal stage, the diagnosis is difficult (especially in the absence of family history) because of the absence of characteristic features and because of the presence of numerous underlying causes for neonatal erythroderma. Gene analyses can offer help in those cases.

ILC is a characteristic migratory polycyclic or annular plaques with double-edged scales and it is pathognomonic for NS. Although this disease is undoubtedly a congenital keratinization disorder, it has clinical and histological similarities to psoriasis. Trichorrhexis Invaginata (TI) (bamboo hair = ball-and-cup hair) results from invagination of the distal part of the hair shaft (ball) into the proximal part (cup).
This invagination occurs at site of intermittent keratinization defect of the hair cortex that makes cortical cells soft. Bamboo hair usually breaks off at a length of 3-4 cm, and usually only a small number of hairs show clear changes so multiple examination is needed. Eyebrow and eyelashes may develop TI even earlier than scalp hair so they are a better choice for sampling. Other hair shaft defects (like pili torti seen in our patient) may be seen as well.

Atopic dermatitis is present in all cases of NS, and most cases have other atopic features like asthma, hay fever, high IgE, eosinophilia and food allergy. Other reported abnormalities in cases of NS including growth retardation, mental retardation, selective antibodies deficiency to bacterial polysaccharides and aminoaciduria.

The main clinical diagnosis in our case was Netherton syndrome (ichthyosis linearis circumflexa in association with atopic eczema and hair shaft defects), which was confirmed by histological examination and laboratory investigations. The differential diagnosis in our patient included erythrodermic atopic and seborrheic dermatitis, psoriasis, nonbullous ichthyosiform erythroderma, zinc/biotin deficiency, protein metabolic disorders, pemphigus foliaceus, congenital erythroderma, erythrokeratodermia, hyper IgE syndrome and other immune deficiency syndromes. These diagnoses were ruled out in our case after appropriate laboratory investigations and in view of the patient’s clinical setting.

Treatment of NS is mostly symptomatic and is aimed at the atopic dermatitis as well as the ichthyotic skin. It is very important to treat each patient according to his clinical presentation, as the clinical features of the disease are varied according to the age: infancy, childhood, and adulthood.

On the whole, emollients, keratlytics and antibiotics are still the mainstay of treatment in patients with NS. In the neonatal period, it is vital to prevent dehydration, temperature instability and infection. If any of these complications occur, it should be treated promptly. Management of atopic dermatitis should start with an assessment of the patient’s individual needs according to their age, sex, social environment, sites of involved skin and severity of disease. The child with a topic dermatitis should wear cotton clothes, and should avoid synthetics and wools, which irritate the skin. Keeping the skin moist is extremely important in managing eczema because the skin is so dry. Atopic dermatitis is characterized by its inherent itch. Antihistamines (e.g. chlorpheniramine maleate, and hydroxyzine hydrochloride) have a role in management because they help the child sleep and break the itch-scratch cycle, if given at a sufficiently high dosage at bedtime.

The goal of treatment of atopic dermatitis is to relieve the itching and to flatten the lichenified lesions. Topical corticosteroids are the gold standard for treating eczema. However, the long term use of topical steroids is a matter of controversy as they may lessen the facial erythema but there is increased risk of systemic absorption because of the defective skin barrier, especially in infants and young children, and when large areas of the body are affected. Therefore, the object of treatment should be to use the lowest potency steroids that achieve the treatment goal. New topical immunomodulators offer an attractive supplement or alternative in certain circumstances. Foods that are known to cause an allergic skin reaction in a specific patient should be avoided. As localized bacterial infection is the most common complication of eczema, any signs of skin infection should be treated promptly, usually by anti-staphylococcal topical and/or systemic antibiotics.
Treatment of the ichthyotic skin is aimed at decreasing the signs and symptoms by hydration, lubrication, and keratolysis. The affected skin has a decreased barrier function and increased transepidermal water loss. Thus, the main approach to treatment includes hydration of the skin followed immediately by the application of lubricants to retain the hydration and softening and to prevent evaporation. Treatment regimens are variable and are in no way restrictive. They may include topical agents, oral medications and/or a combination. 

Keratolytic creams and lotions used for ichthyosis may contain 10–20% urea, propylene glycol, alphahydroxy acids, or salicylic acid. However, because of the impaired barrier function in ichthyosis, a widespread use of topical salicylic acid or urea over large areas of body surface can lead to possible systemic absorption and toxicity. These preparations are better avoided in infants and young children.

Topical retinoids like tretinoin and tazarotene are beneficial in the treatment of ichthyosis but can be irritating in some patients. However, patients may complain of increased irritation as well as flares of their associated/concomitant atopic dermatitis. Systemic retinoids are not usually helpful as they may cause deterioration of the skin lesions, although there is one report of response to low dose acitretin. Topical calcipotriol, a synthetic vitamin-D₃ derivative, inhibits hyperproliferation and stimulates differentiation of keratinocytes. It has been reported to be used successfully in one patient, but long term efficacy and safety in NS should be assessed before adopting the treatment, as there may be a risk of hypercalcemia with the use of topical calcipotriol, especially when large areas of the body are involved. PUVA therapy (psoralen plus ultraviolet light A) has been reported to be beneficial in one patient with NS.

Topical tacrolimus and pimecrolimus are immunomodulatory drugs successfully used for atopic dermatitis and tacrolimus which have been reported to be useful in patients with NS and in atopic dermatitis for children as young as 2 years of age. Dramatic clinical improvement using 0.1% tacrolimus ointment has been reported in patients with isolated ichthyosis linearis circumflexa and as part of Netherton syndrome. Systemic absorption occurred in the treated children, however, and tacrolimus blood levels were within or above the established therapeutic trough range for oral tacrolimus, but no signs or symptoms of toxicity developed. Therefore, the dosage and application regimen of these drugs in patients with NS should be further clarified.

In conclusion, our case of Netherton's syndrome highlights the need for proper follow up and investigation in all pediatric patients presenting with seemingly resistant or unusual dermatitis-like skin lesions. New therapies may offer in the future some relief to the affected patients, and new laboratory methods promise prenatal diagnosis in families with members affected by NS.
References


Conductive Hearing Loss in Systemic Lupus Erythematosus: A Case Report with Review of Literature

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Abstract
A 33 year-old white man with signs and symptoms of Systemic Lupus Erythematosus (SLE) confirmed by laboratory, serological and immunological tests. The patient developed typical picture of Conductive Hearing Loss (CHL) of otosclerosis 3 years after diagnosis of SLE. Previous studies reported association of Sensorineural Hearing Loss (SNHL) and SLE. The purpose of this report is to describe the first case of bilateral CHL in association with SLE. Relevant literature was reviewed and possible autoimmune involvement of middle ear was speculated.

Keywords
Conductive hearing loss, otosclerosis, systemic lupus erythematosus.

Introduction
Systemic Lupus Erythematosus (SLE), the prototype immune complex disorder, is a multisystem disease affecting the connective tissue (collagen) of unknown etiology. It is characterized by the presence of autoantibodies, and the circulating immune complexes can produce immunologically mediated tissue injury to multiple organs including skin, kidneys, heart, lung, joints, central nervous system and serosal surfaces. However, otologic involvement in SLE has been reported and it was confined only to the inner ear with the end result of sensorineural hearing loss. It does not appear in the literature that there are any reports on the association between Conductive Hearing Loss (CHL) and SLE.

The present report concerns a white man who had clinical and serological findings of SLE whose otological examination and hearing evaluation revealed typical picture of bilateral CHL of otosclerosis.

Case Reports
A 33 year old white Jordanian man was diagnosed to have SLE. The diagnosis was established on the basis of polyarthritis, renal disease, positive skin biopsy, hemolytic anemia with leucopenia, positive Antinuclear Antibodies (ANA), pericardial serositis, gingival bleeding and ulcers, facial rash, elevated Erythrocyte Sedimentation Rate (ESR), and present immune complexes.

Clinical Profile: The patient has been well during the past two years, complained of rash around his mouth and gums, moderate retrosternal pain when lying in bed, intermittent fever, flitting arthralgia and an episode of pericarditis. The patient was hospitalized for loss of appetite with loss of weight of about 11 Kg in the last month, polyarthralgia, rash over the chest and face and recurrent fever. Two weeks prior to admission, he had abdominal pain, nausea and vomiting. On physical examination, he looked pale and ill-appearing. Temperature 40.4°C; gingivitis; red macular rash over trunk, face, neck and arms; large mobile lymph node in the right axilla and a smaller one in the left axilla; small node in the left neck; blood pressure 110/70 mm Hg; pulse 120 regular; and the rest of examinations were normal. No evidence of infection was found what so ever. Sternal bone marrow, right quadriceps muscle biopsy, lip biopsy excluded malignancy, polyarteritis nodosa and Sjogren’s syndrome, respectively. Chest and abdominal x-rays were normal. Biopsy of lymph nodes showed reactive hyperplasia. Kidney biopsy was suggestive of tubulo-interstitial disease. Skin biopsy showed mild vasculitis.
**Laboratory Findings:** Diagnostic laboratory and serological tests disclosed a White Blood Cell (WBC) count of 4000, hemoglobin 8 gm/dl ml blood, hematocrit 33%, platelets 180,000/mm³, ESR 114 mm/hour, serum creatinine 4.1 mg/dl, blood urea nitrogen (BUN) 114 mg/dl, uric acid 9.3 mg/dl, Na⁺ 131 mM, K⁺ 5.5 mM, HCO₃⁻ 17.3 mM, Calcium 8.6 mg/dl, total serum protein 9.0 gm/dl with albumin 3.3 gm/dl. Urinalysis revealed a specific gravity of 1.010, WBC 8-10. The ANA was speckled with a titer of 1:1280, cryoglobulins strongly positive, immune complexes were present, C₃ 62 mg/dl (normal 60-130), C₄ 8 mg/dl (normal 12-42), the anti-DNA was negative, the LE cells was negative. Liver function tests were normal. The final diagnosis was SLE with episode of pleural effusion. The patient was treated with prednisolone 60 mg daily with remission of symptoms and improved renal function (creatinine 1.2 mg/dl). The dose was reduced to 20 mg per day and since then he had many episodes of exacerbation of the disease.

**Audiologic Findings:** The patient presented to the audiology clinic complaining of gradual loss of hearing over the last 3 years after the diagnosis of SLE disease. He complained of bilateral gradual hearing loss and tinnitus in both ears. There was no history of vertigo or other otologic diseases. Routine Ear- Nose- Throat (ENT) examination was normal, Rinne tests were negative on both sides and Weber test in the center. His initial audiogram revealed a moderate conductive hearing loss of 48 and 50 dB pure tone average at 500 to 4000 Hz at the right and left ears, respectively. The second audiogram was taken six months later showed further deterioration of hearing, 52 and 54 dB conductive loss at the right and left ears, respectively (Fig. 1). The smallest air-bone gap was noted at 2000 Hz, while the gap was wider above and below. Bone conduction levels showed mild loss at 2000 and 4000 Hz and were higher than the previous levels. Speech tests were consistent with moderate conductive hearing loss bilaterally. Impedance audiometry showed reduced compliances (0.3 ml) bilaterally (Fig. 2). Both ipsi-lateral and contra-lateral acoustic reflexes were absent. Bithermal caloric tests showed normal vestibular responses at both ears. Recruitment and tone decay tests showed no abnormalities.

Brain stem which evoked response audiometry was consistent with conductive hearing loss bilaterally. Exploratory tympanotomy was suggested and the patient did not show up since then.

Figure (1): Audiogram showing bilateral moderate conductive hearing loss.

Figure (2): Tympanogram showing bilateral low compliance of tympanic membranes.
Discussion

SLE is a chronic autoimmune disease characterized by B-cell hyperactivity and can affect virtually any organ system. Autoimmunity to type II collagen is found in many diseases including rheumatic arthritis, relapsing polychondritis, systemic sclerosis, polyarteritis nodosa, Cogan’s syndrome and Sjögren’s syndrome. Otosclerosis, which is a disorder of the human otic capsule and stapes, has been reported to be caused by autoimmune reaction to type II collagen as a major cause. 9-11 This type of disorder causes CHL. SLE has been reported to be associated with Sensorineural Hearing Loss (SNHL). 5-8,12,13 Kastanioudakis et al 14 reported SNHL in 8 patients and unilateral CHL in 1 patient out of 38 screened SLE patient. This author did not mention the pathology lying behind the CHL in his patient. The case reported here is the first of bilateral CHL, probably due to autoimmune otosclerosis, in association with SLE in which otological examination and audiological findings were highly suggestive to otosclerotic disorder. This patient has negative family history of CHL of any type or otosclerosis.

The stimulus behind the development of autoimmune disorders remains unknown. In SLE, there is an excessive production of autoantibodies resulting in Immune Complex (IC) formation leading to inflammation and tissue damage 15,16 with local IC deposition in many cases 16 and infiltration with destruction and fibrosis. The occurrence of SLE and CHL (middle ear structure involvement) in this reported case raises the question of association or coincidence. Supportive evidence for this association comes from the results of many studies on SLE patients: deposits of immunoglobulins (IgG, IgM, and IgA) and complement C3 were present along the resorption lacunae besides osteocytes and chondrocytes around the destructive process of the otic capsule and otosclerotic stapes, 17,18 granular deposition of IgM, IgG and fibrin in involved skin 19 significant Temporomandibular Joint (TMJ) involvement secondary to osteoarthritis 20 and other joints deformities typical of SLE arthritis, 21, 22 nodules in tendons with fibrous material, 23 periarticular or diffuse osteoporosis, 24 and periarticular and soft tissue calcification. 24, 25

The etiopathogenetic mechanism of otosclerosis is not fully understood and is believed to be a multifactorial disorder: hereditary and genetic causes have been widely accepted in the development of otosclerosis and account for 50 percent of cases 26 autoimmunity reaction to type II collagen has been reported as a major cause of otosclerosis 9-11 and a strong association between measles virus and otosclerosis. 27-29

In light of the results of previous studies 9-11,17-25 and the history and findings in this reported case: middle ear ossicular joints, muscles, tendons, and stapes footplate could be a target for SLE induced disease. Although conclusive evidence is lacking, audiologic manifestation of CHL in this SLE patients could be due to IC deposition in middle ear structures and infiltration with destruction and fibrosis in the region between bone and cartilage of the otic capsule and footplate of stapes resembling otosclerotic process, autoimmune osteoarthrosis of the middle ear ossicular joints, or middle ear soft tissue (muscles and tendons) and periarticular calcifications.

In conclusion, whatever the cause of CHL, the observation and findings in this patient suggest that the association of middle ear involvement, probably autoimmune otosclerosis, with SLE has not been previously reported. Further investigation on temporal bones, specimens of similar cases and exploratory tympanotomy are needed to better delineate the pathologic characteristics of middle ear involvement in SLE. The question of whether CHL due to middle ear autoimmune involvement and SLE are somehow linked remains intriguing but unanswered.

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References


Herpes Gestations: A Case Report

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Abstract

A 34 year old female, presented to our dermatology clinic with pruritic polymorphous vesicles, papules and bullae during her 16 week of pregnancy which was the sixth pregnancy. She was diagnosed on clinical and histopathoogical bases to have “Herpes Gestations.” There was no previous history of Herpes Gestations (H.G) in previous pregnancies. She was started on prednisolone 5mgm/tablet, 30 mgm daily, which led into lesion clearing.

She delivered a normal baby and the steroid was tapered and then was stopped two weeks after delivery.

The importance of this presentation is to keep in mind the possibility of the occurrence of this disease during pregnancy.

Case Report

A 34-year – old pregnant woman, who is gravida 6 para 4 + one abortion, presented to our dermatology clinic with pruritic polymorphous vesiculo bullous lesions that started at the 16th week of gestation. It appeared first on the umbilicus then spread as erythematous annular over the extremities laboratory investigation which showed normal data. The patient was treated with steroid which cleared all lesions the baby was born normal and the mother too.

Keywords

Herpes Gestations.

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