

Case 1

Clinical Data

A 48-year-old male presented with recurrent bouts of non-itchy wheals with fever, chills, and malaise, lasting almost 24 h. Onset started during infancy. Examination revealed multiple large plaques showing hyperpigmentation, hypertrichosis, and induration (Figs. 2.1, 2.2, and 2.3). He had history of recurrent cellulitis, joint pain, and progressive hearing loss.

Differential Diagnosis

- **Morphea:**
 - Shows indurated plaques, but usually without hypertrichosis.
 - Not associated with systemic symptoms of fever, chills and malaise.
 - No loss of hearing.
- **Kaposi Sarcoma:**
 - Shows brown erythematous hyperpigmented plaques, but without hypertrichosis.
 - No systemic symptoms and
 - No loss of hearing.
- **Winchester Syndrome:**
 - Skin changes of thickenings, hyperpigmentation, and hypertrichosis.
 - Shows dwarfism (unlike this case), joint contracture among other anomalies.
- **POEMS Syndrome:**
 - Skin changes of thickenings, hyperpigmentation, and hypertrichosis.
 - Other elements of the syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, M-Paraproteinemia and Skin lesions) are usually seen.
- **Muckle Wells Syndrome:**
 - Bouts of urticaria, fever, and chill (like this case).
 - Progressive hearing loss (like this case).



Fig. 2.1 Erythematous hyperpigmented plaques on both legs. The lesions show hypertrichosis



Fig. 2.2 Erythematous plaques over the left breast



Fig. 2.3 Faint, erythematous urticarial eruptions on the trunk

Biopsy Findings (of Case 1)

Biopsy findings were of mild epidermal hyperplasia, remarkable dermal thickening replacing the subcutaneous fat, dilated blood vessels, perivascular and interstitial infiltrate of plasma cells, eosinophils and mast cells with large numbers of spindle-shaped cells (Figs. 2.4, 2.5, 2.6, and 2.7).

Investigations

- Lab investigations:
 - ESR: High.
 - CRP: High.
 - Serum amyloid protein (SAP): High.
 - Interleukin-6: High.
- Radiological investigations:
 - Abdominal Sonography: Hepatosplenomegaly.
- Other investigations:
 - Hearing test: Impaired hearing.

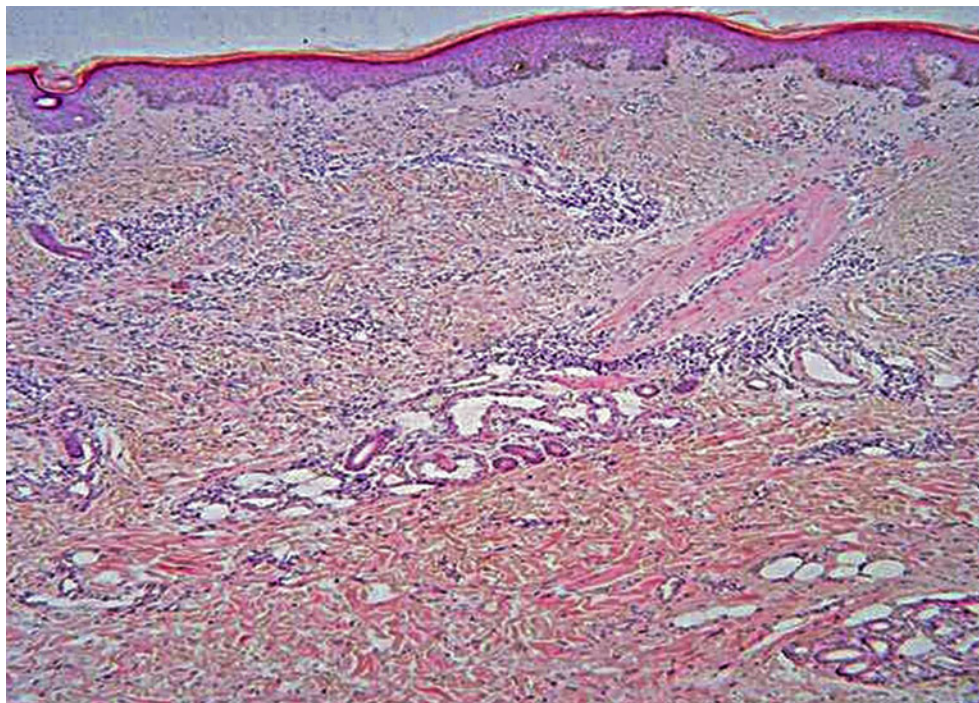


Fig. 2.4 Mild epidermal hyperplasia, remarkable dermal thickening replacing the subcutaneous fat

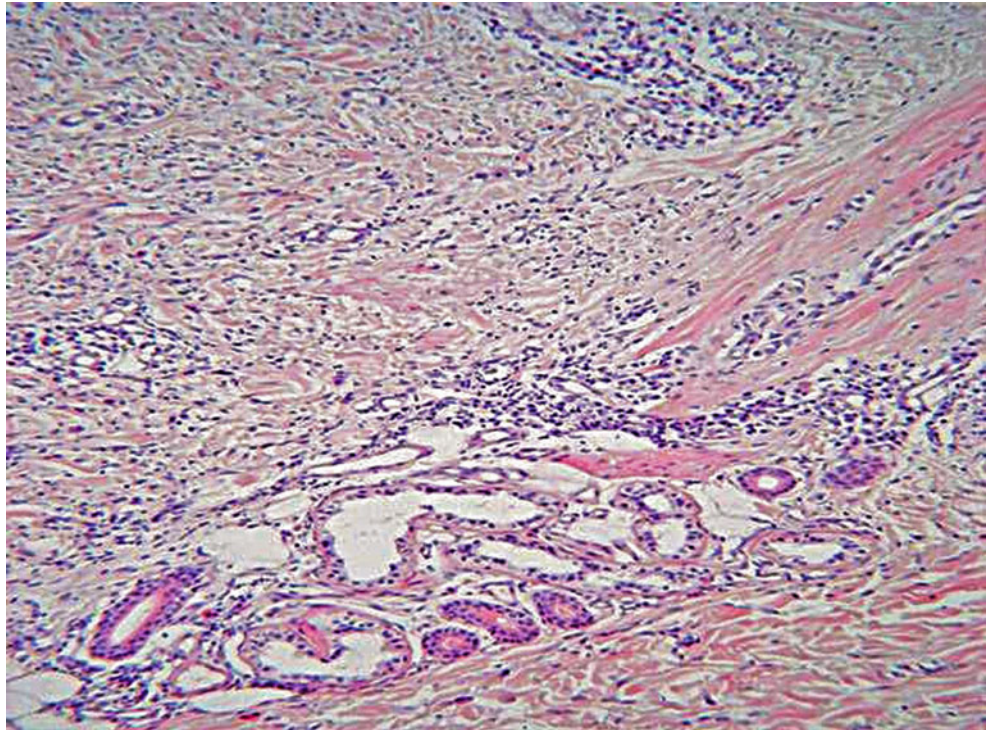
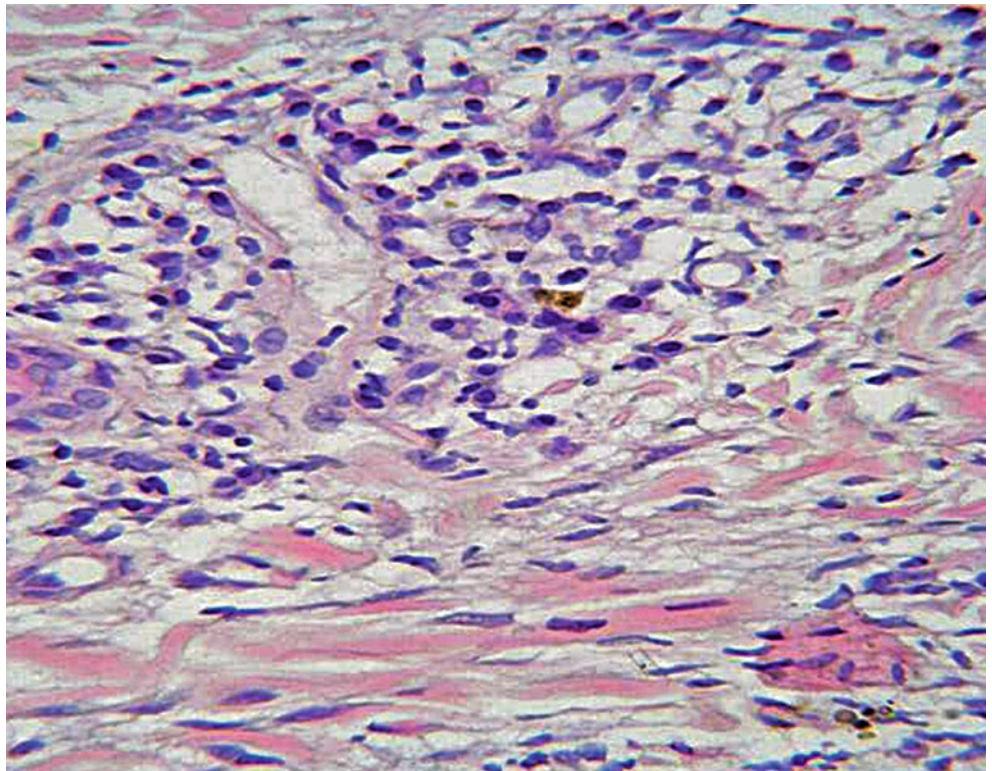
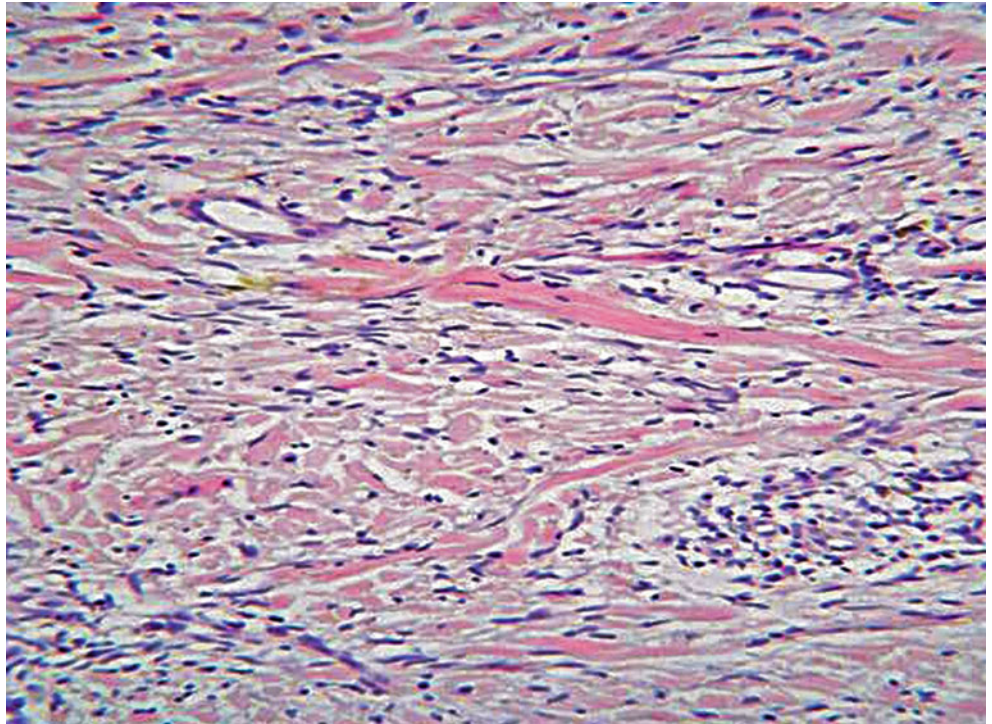
Fig. 2.5 Dilated blood vessels**Fig. 2.6** Perivascular and interstitial infiltrate of plasma cells, eosinophils and mast cells. Large numbers of spindle-shaped cells are seen

Fig. 2.7 Spindle cell (fibroblast) infiltration



Case 2

A 12-year-old male with similar clinical presentation to Case 1. His skin showed erythematous hyperpigmented plaques on both legs (Fig. 2.8).

Biopsy Findings (of Case 2)

Biopsy findings revealed remarkable dermal thickening with replacement of the subcutaneous fat (Fig. 2.9), dense perivascular and interstitial mononuclear cell infiltrate (Fig. 2.10). Higher power showed diffuse infiltration with plasma cells, mast cells, and eosinophils (Fig. 2.11).



Fig. 2.8 A 12-year-old male with similar clinical presentation to Case 1. His skin showed erythematous hyperpigmented plaques on both legs

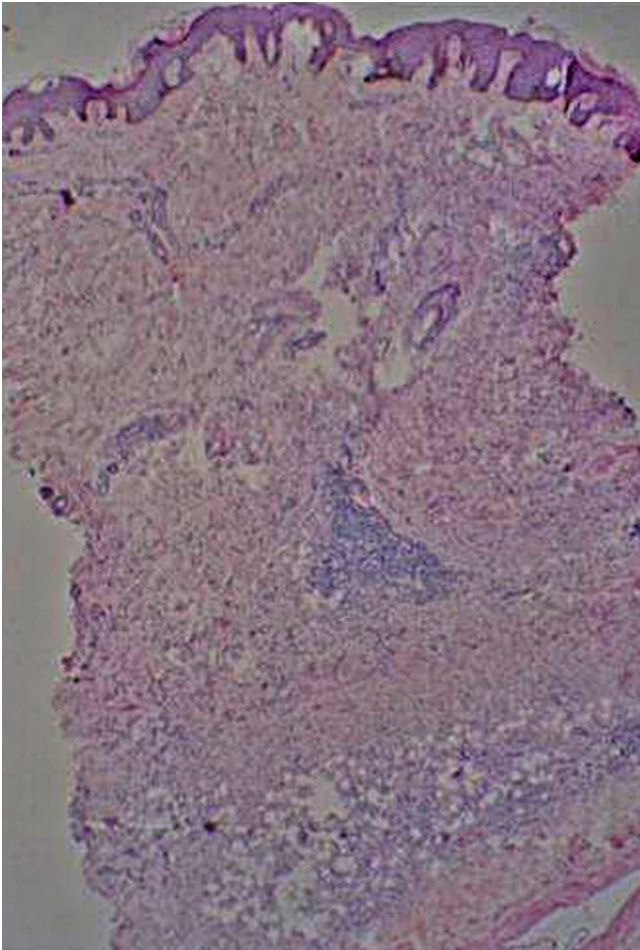


Fig. 2.9 Remarkable dermal thickening with replacement of the subcutaneous fat

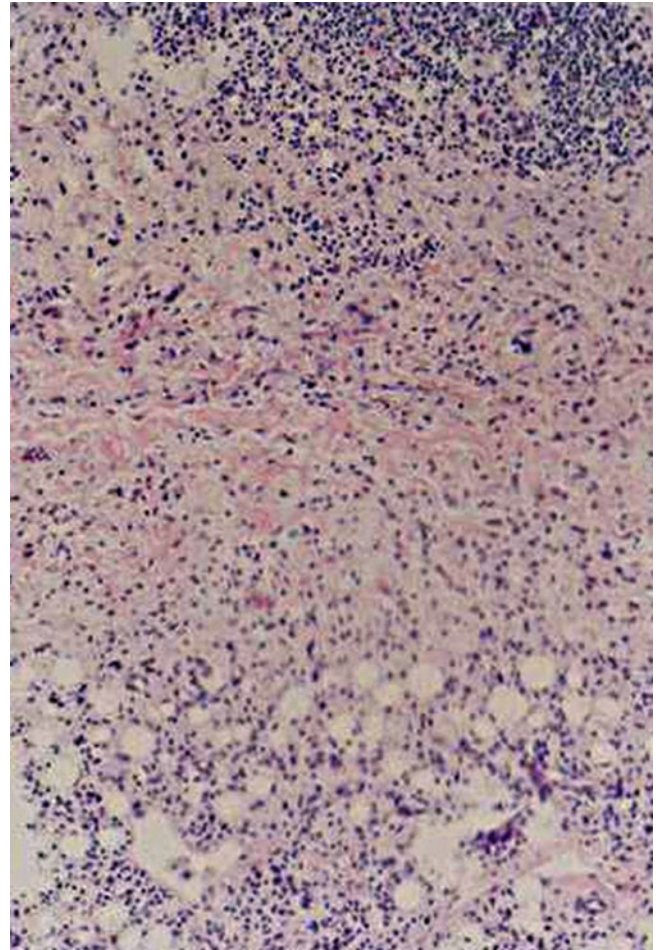


Fig. 2.10 Dense perivascular and interstitial mononuclear cell infiltrate

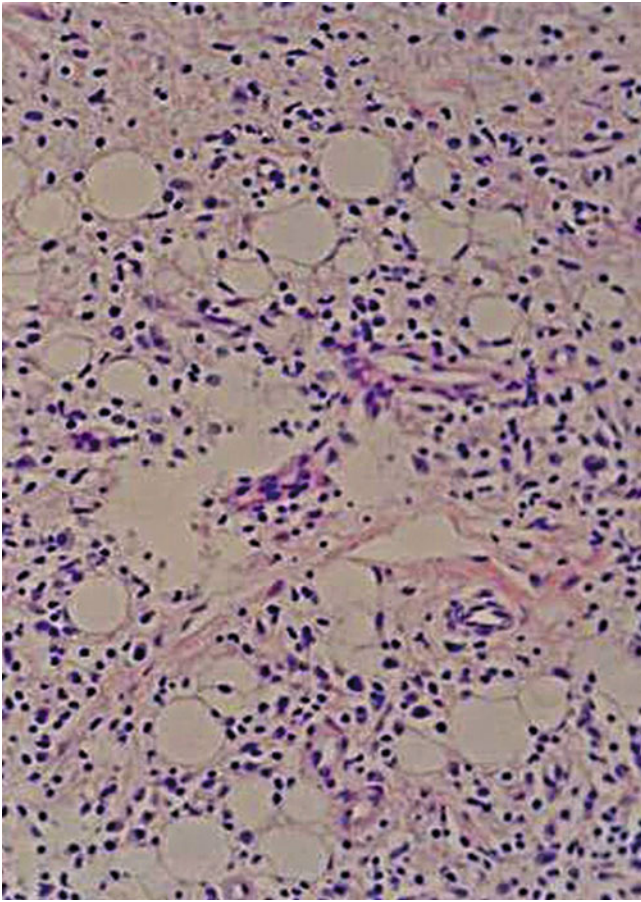


Fig. 2.11 Diffuse infiltration with plasma cells, mast cells, and eosinophils

Case 3

A 6-year-old male with similar clinical presentation to Cases 1 and 2. His skin showed large hyperpigmented and

indurated plaques occurring on the legs, thighs, and genital area (Figs. 2.12 and 2.13). The marked induration on the genital area resulted in retraction of the penis.



Figs. 2.12 and 2.13 A 6-year-old male with similar clinical presentation to Cases 1 and 2. His skin showed large hyperpigmented and indurated plaques occurring on the legs, thighs, and genital area. The marked induration on the genital area resulted in retraction of the penis

Biopsy Findings (of Case 3)

Biopsy findings revealed marked thickening of the dermis. The subcutaneous tissue was replaced by thick collagen, and

the thickening was associated with a perivascular and interstitial mixed cellular infiltrate (Figs. 2.14 and 2.15). Higher power showed fibroblasts, plasma cells, eosinophils and mast cell infiltrate (Fig. 2.16).

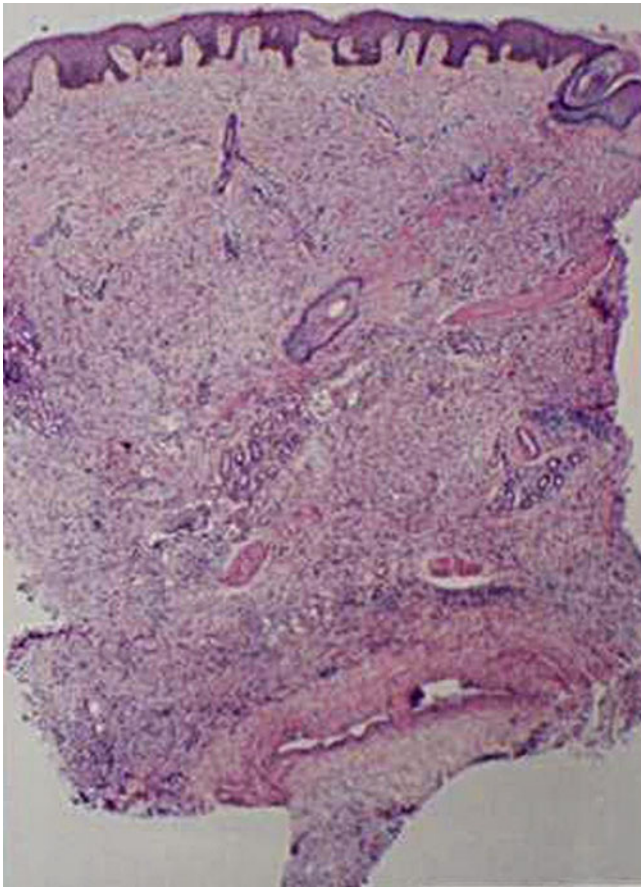


Fig. 2.14 Marked thickening of the dermis. The subcutaneous tissue is replaced by thick collagen and is associated with a perivascular and interstitial mixed cellular infiltrate

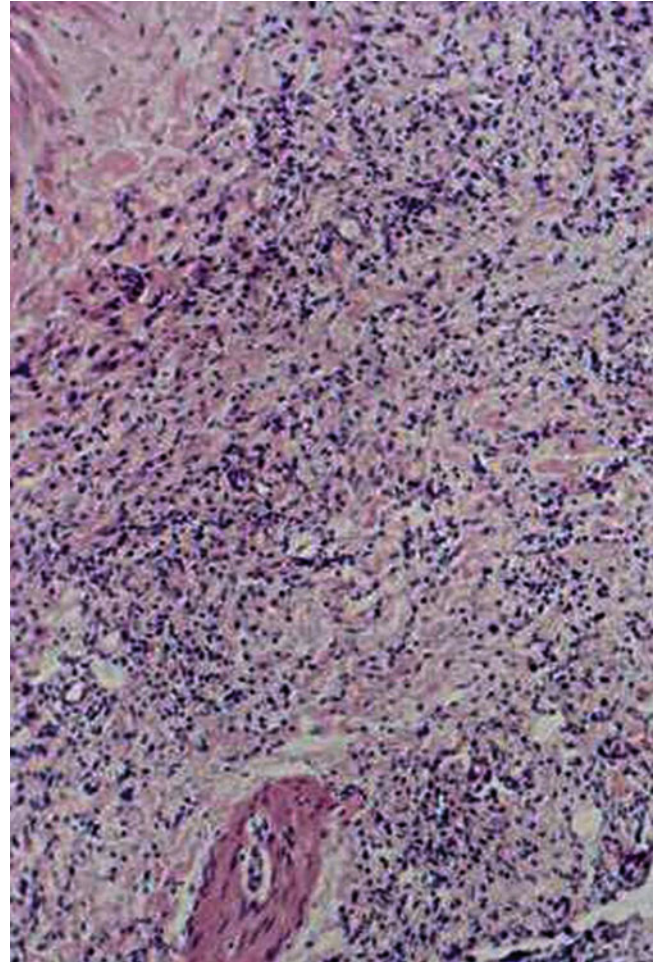


Fig. 2.15 Thickening is associated with a perivascular and interstitial mixed cellular infiltrate

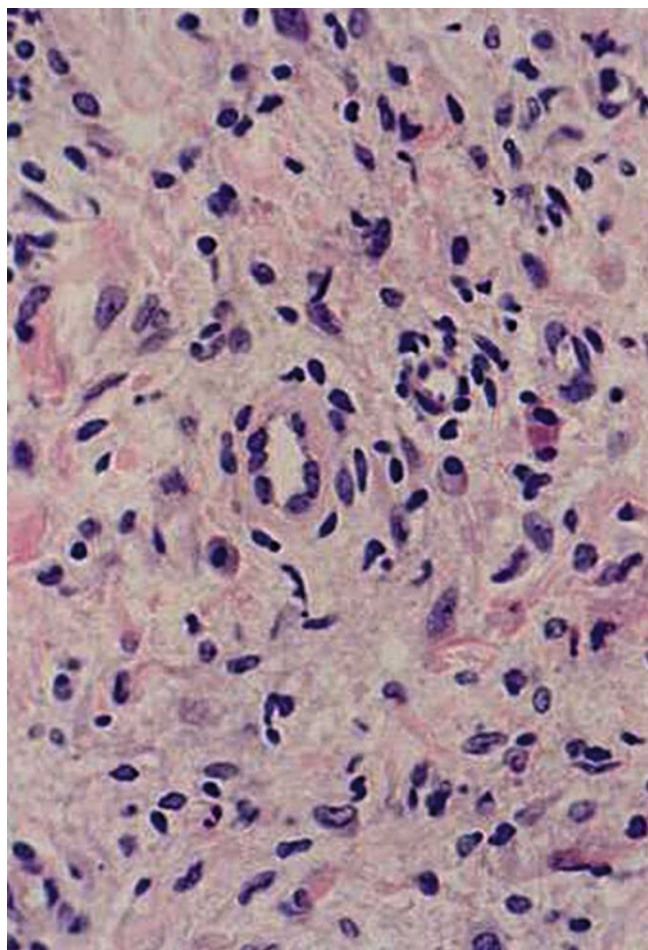


Fig. 2.16 Higher power of the infiltrate showing fibroblasts, plasma cells, eosinophils and mast cells

Case 4

A 30-year-old female with similar clinical presentation to Cases 1, 2, and 3. Her skin showed large sclerotic and

hyperpigmented plaques involving the abdomen and the forearm and large sclerotic and hyperpigmented plaques involving lower extremities and buttocks (Figs. 2.17, 2.18, 2.19, and 2.20).



Figs. 2.17 and 2.18 A 30-year-old female with similar clinical presentation to Cases 1, 2, and 3. Her skin showed large sclerotic and hyperpigmented plaques involving the abdomen and the forearm



Figs. 2.19 and 2.20 Large sclerotic and hyperpigmented plaques involving lower extremities and buttocks

Biopsy Findings

Biopsy findings revealed remarkable dermal thickening (Fig. 2.21), perivascular and interstitial mononuclear cell

infiltrate (Fig. 2.22) and degenerated elastic fibers (Fig. 2.23).

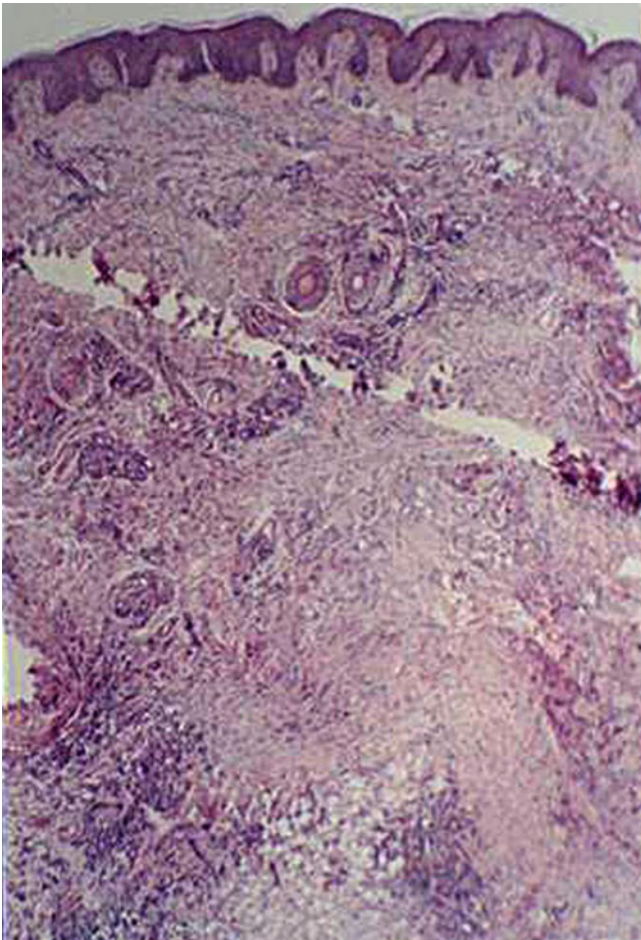


Fig. 2.21 Remarkable dermal thickening

Fig. 2.22 Perivascular and interstitial mononuclear cell infiltrate

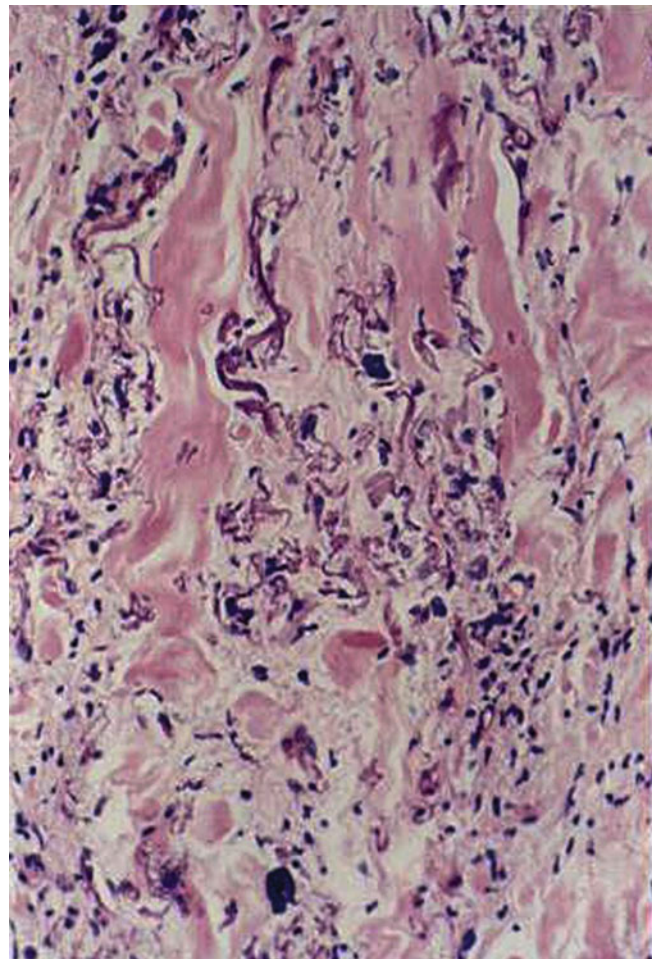
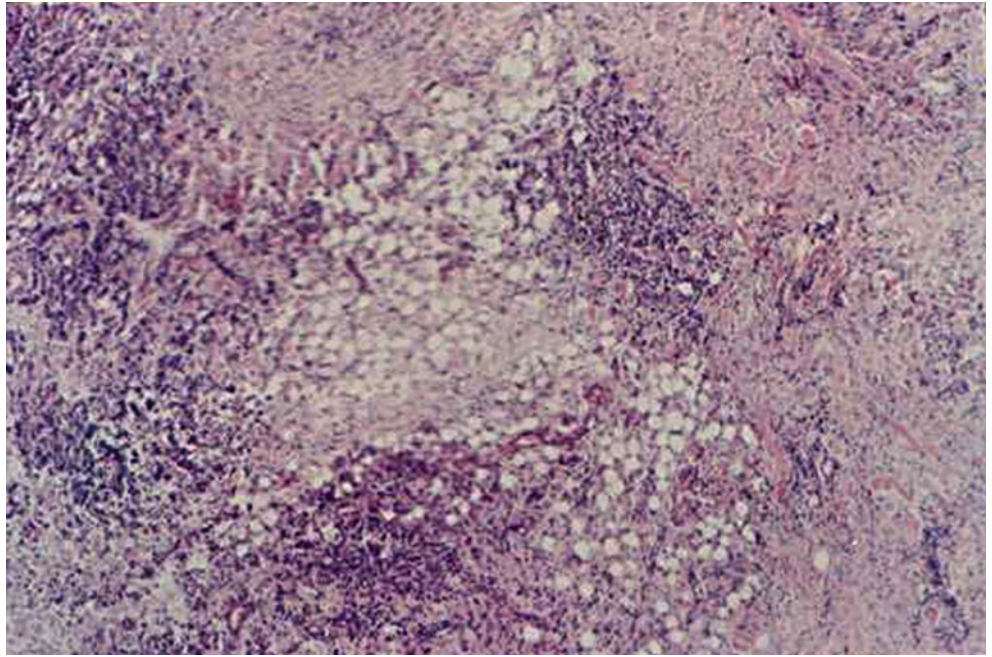


Fig. 2.23 Degenerated elastic fibers

Based on the Following Findings (in All the Cases)

- Onset at infancy.
- History of recurrent urticaria with fever and chills.
- Recurrent arthritis and cellulitis.
- Progressive deafness.
- Skin lesions of large plaques showing hyperpigmentation, hypertrichosis and induration.
- Elevated ESR, CRP, and ASP.

The Final Diagnosis of all the four cases was Muckle-Wells Syndrome (MWS).

About the Diagnosis

Definition

- Muckle-Wells Syndrome (MWS) is a rare auto-inflammatory disorder that belongs to a group of hereditary febrile syndromes. It is characterized by recurrent and self-limited episodes of fever, urticaria, arthralgia, myalgia and conjunctivitis since childhood. The symptoms are related to exposure to cold temperatures. Progressive sensorineural deafness develops, as does amyloidosis in about one-third of patients.
- MWS was first described in 1962 by Thomas James Muckle and Michael Vernon Wells.
- Indurated skin with hypertrichosis and hyperpigmentation was recently described as a skin manifestation of Muckle Wells Syndrome (El-Darouti et al. 2006).

Epidemiology

- MWS is a rare disorder.
- It has been reported in many regions of the world, but its prevalence is unknown.

Pathogenesis and Etiology

- MWS is inherited as an autosomal dominant trait with variable expression within a family and from one family to another.
- The gene responsible for MWS was localized to chromosome 1q44.
- It has been demonstrated that MWS is associated with mutations in the NLRP3 gene (also known as CIAS1 gene), which codifies cryopyrin, a protein responsible for regulating the production of proinflammatory cytokines, such as interleukin-1 β .

- The possible deficiency of inflammatory cascade inhibitors or the cytokine receptor abnormalities may explain both the marked elevation of IL-6 and proinflammatory mediators and can cause recurrent inflammation of the skin that may eventually lead to increased production of growth factors and subsequent thickening of the epidermis, dermis, and subcutaneous tissue.
- The constant finding of perivascular and interstitial mixed inflammatory infiltrate of plasma cells, histiocytes, eosinophils, and mast cells is an important indicator of the inflammatory nature (probably mediated by IL-6) of the skin lesions.
- The elevation of IL-6 in MWS can act as an osteoclast activating factor which may eventually cause destruction of the corti organ leading to sensorineural deafness and by a similar mechanism cause the persistent arthritis.
- MWS is closely related to two other syndromes, familial cold urticaria and neonatal onset multisystem inflammatory disease. All three are related to mutations in the same gene and subsumed under the term cryopyrin-associated periodic syndromes (CAPS).

Clinical Features

- The disease starts during childhood and adolescence with:
 - Recurrent bouts of urticaria with chills, fever and malaise, lasting 24 h.
 - Arthritis (painful joints).
 - The urticaria may start from birth and may occur daily throughout life.
 - There may be actual wheals or sometimes only macular erythema.
- Over the next two to four decades:
 - Sensorineural deafness occurs in almost all patients.
 - progressive nephropathy due to amyloidosis occurs in 30 % of patients.
- Previously reported associations:
 - Conjunctivitis.
 - Angioedema.
 - Meningitis.
 - Limb and face deformities.
 - Ichthyosis.
 - Aphthosis.
 - Mental retardation.
 - Growth retardation.
 - Decreased fertility.
 - Hepatosplenomegaly.
- New findings in all the presented cases:
 - Remarkable sclerosis associated with:
 - Hyperpigmentation and Hypertrichosis.

Tip

- Indurated skin with hypertrichosis & hyperpigmentation was recently described as a skin manifestation of Muckle-Wells Syndrome (El-Darouti et al. 2006).

Tips

- Peculiar skin lesions of induration, hypertrichosis and hyperpigmentation were previously reported under different titles (The H-syndrome, Plasma-cell panniculitis). Authors of both papers have found, in addition to the above skin lesions, deafness, hepatosplenomegaly, high ESR, and identical histopathology to MWS.
- None of the authors measured the levels of ASP or IL-6.
- It was proposed that these unique features represent a variant of Muckle-Wells syndrome (El-Darouti 2009).

Histological Features

- Epidermal hyperplasia with marked thickening of the dermis. The subcutaneous tissue is replaced by thick collagen.
- Perivascular and interstitial infiltrate of plasma cells, eosinophils and mast cells. Large numbers of spindle-shaped Fibroblasts are seen.
- As amyloid deposition is a feature of MWS, the biopsy may show:
 - Deposits of amorphous eosinophilic, fissured material.
 - Positive stains for amyloid: Congo red, thioflavin T, scarlet red, and PAS.

Investigations

- Lab tests:
 - C-reactive protein (CRP): High.
 - ESR: High (more than 100 in the second hour).
 - Serum amyloidosis A protein (SAP): High.
 - IL-6: High.
 - Leukocytosis.
 - Disturbed kidney function tests owing to progressive nephropathy due to amyloidosis.
- Radiological investigation:
 - Renal imaging may be indicated in selected cases.
- Other investigations:
 - Tests for sensory deafness is mandatory.

Differential Diagnosis

- **Morphea:**
 - Shows indurated and sclerotic plaques, but without hypertrichosis.
 - Hyperpigmentation occurs in late atrophic lesions.

- Not associated with systemic symptoms of fever, chills and malaise.
- No loss of hearing.
- **Kaposi's Sarcoma:**
 - It may show erythematous brown plaques.
 - Histopathologically interstitial infiltrate of spindle cells Stains positively with CD34 and factor VIII.
 - No hypertrichosis.
 - No systemic symptoms and no loss of hearing.
- **Mastocytosis:**
 - Presents with hyperpigmentation but no hypertrichosis.
 - Histopathology shows mast cells.
- **Winchester Syndrome:**
 - Skin changes of thickenings, hyperpigmentation, and hypertrichosis usually occurs but shows:
 - Dwarfism, joint contracture among other anomalies.
- **POEMS Syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, M Paraproteinemia & skin lesions):**
 - Skin changes of thickenings, hyperpigmentation, and hypertrichosis may occur.
 - Organomegaly is a feature.
 - There are other elements of the syndrome (polyneuropathy and endocrinopathy, M paraproteinemia, glomeruloid hemangioma, and edema).
- **Becker's nevus:**
 - It features hyperpigmentation and hypertrichosis, however:
 - There is no sclerosis.
 - It is histopathologically different.
- **Familial Mediterranean fever:**
 - Presents with periodic fever, abdominal pain, erysipelas-like lesions and urticaria but it's not associated with the characteristic sclerotic hyperpigmented plaques and not associated with deafness.
- **Schnitzler syndrome:**
 - Chronic, urticaria with recurrent fever, bone pain and arthritis, however there is no hyperpigmented and hypertrichotic sclerotic plaques.
 - Monoclonal immunoglobulin M (IgM) gammopathy.
- **Still's syndrome (systemic-onset juvenile rheumatoid arthritis):**
 - Presents with fever, arthritis, hepatosplenomegaly.
 - It, furthermore, features sore throat, lymphadenopathy, pleuritis and pericarditis.
 - No deafness or sclerotic hyperpigmented plaques.

Definite Diagnosis

- The diagnosis of MWS is purely clinical; however, genetic diagnosis is currently feasible.
- Supportive findings are increased ESR, CRP, SAP, and IL-6.

Prognosis

- Over the time, MWS can lead to two main complications:
 - Sensorineural deafness.
 - progressive nephropathy due to amyloidosis.

Treatment

- Potential treatment is the human interleukin-1 beta receptor antagonist; anakinra, (suggesting that IL-1 is a key cytokine for disease expression in individuals with CIAS1 mutations).
- Anakinra was observed to be associated with good results, even an improvement in the hearing loss and amyloidosis when introduced at an early stage.
- Other therapeutic options are: the anti-histaminics, thalidomide, colchicine, corticosteroids and phototherapy (for the sclerotic plaques).

Management of These Cases

In these cases, the author had attempted treatment of the skin lesions and arthritis with colchicine and ultraviolet A light phototherapy (3 times/week), with two cases showing 50 % improvement of the indurations after 8 weeks.

Message

- Sclerotic hyperpigmented and hypertrichotic skin plaques are rare and recently described skin manifestation of Muckle-Wells Syndrome (MWS) that seems from the reported cases to occur exclusively in Orientals.
- Clinically suspected diagnosis of MWS can be verified by biopsy and lab investigations of ESR, IL-6, and serum amyloidosis-A protein (SAP).

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<http://www.springer.com/978-1-4471-4248-5>

Challenging Cases in Dermatology

El-Darouti, M.A.

2013, XV, 763 p., Hardcover

ISBN: 978-1-4471-4248-5