Vascular Interferonopathy Syndromes in Patients with Inherited Mitochondrial Disorders

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I have no financial disclosures

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Case #1

A 27-year-old female with an EARS2-related mitochondrial disorder developed bilateral lower extremity purpuric lesions over 24 hours. A punch biopsy of one of the lesions was performed.

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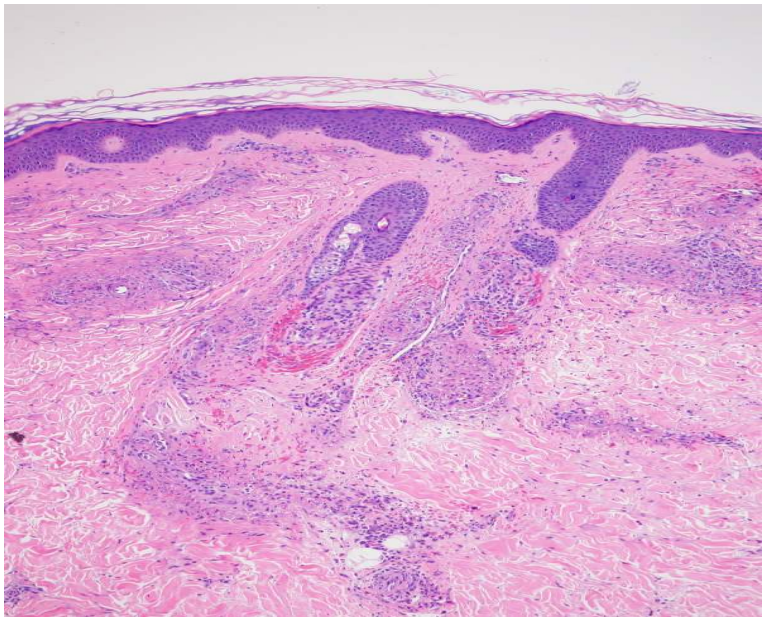
Punch Biopsy



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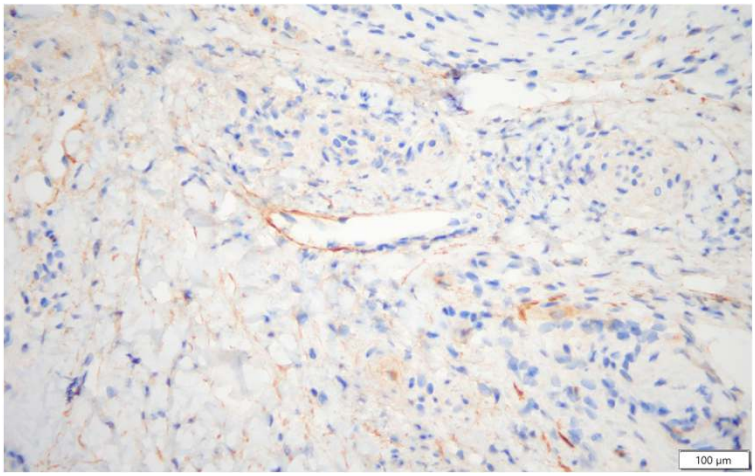
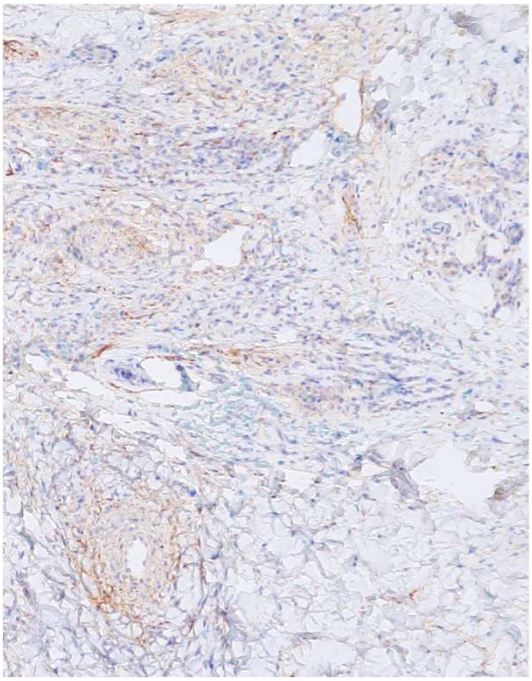
C3d and C4d





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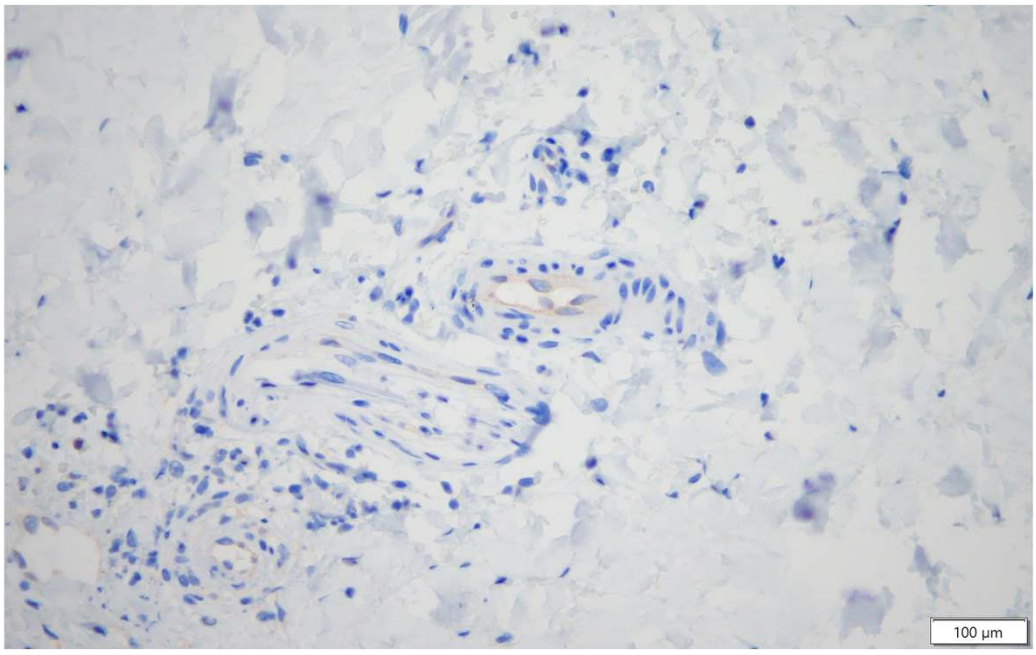
MxA



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DIAGNOSIS:
A. SKIN:Right leg H&E:
-MODERATELY SEVERE LEUKOCYTOCLASTIC VASCULITIS, LIKELY REFLECTING AN ARTHUS TYPE-III IMMUNE COMPLEX REACTION IN THE SETTING OF AN ENHANCED TYPE-I INTERFERON MICROENVIRONMENT POTENTIALLY TRIGGERED BY CYTOPLASMIC MITOCHONDRIAL DNA

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Case #2

A 31-year-old male presented with acral based papular lesions for several months.

Additionally, the patient had been healthy up until his twenties, when he started experiencing muscle pain and weakness with exertion, as well as generalized muscle atrophy.

He had also developed clinical features of a recurrent compartment syndrome.

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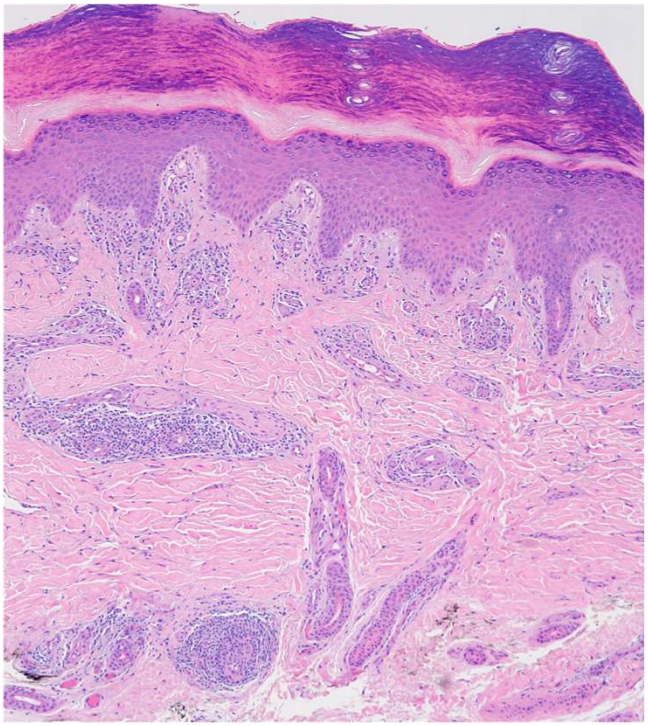
Punch Biopsy



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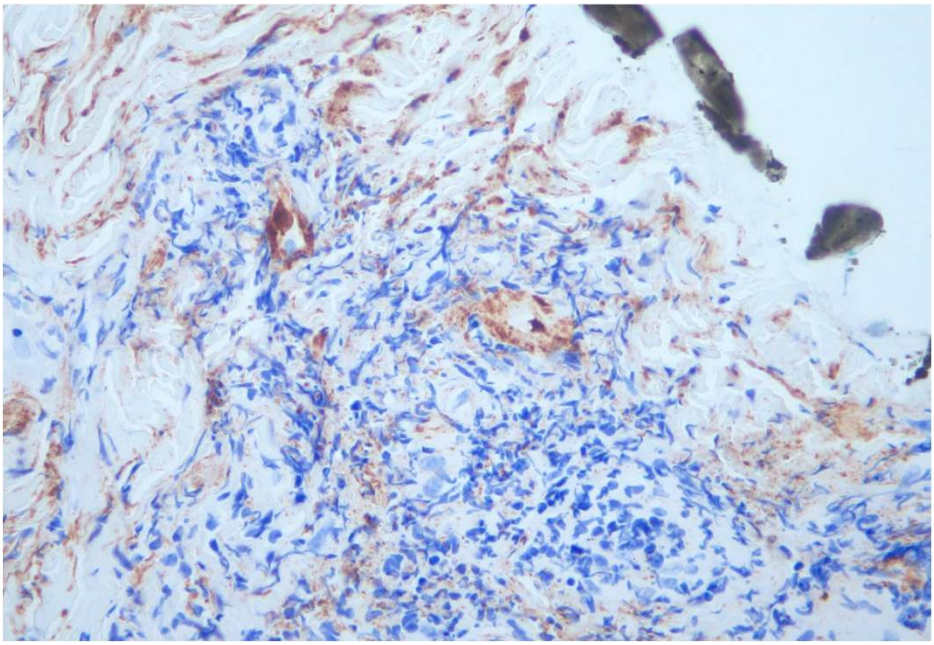
C5b-9



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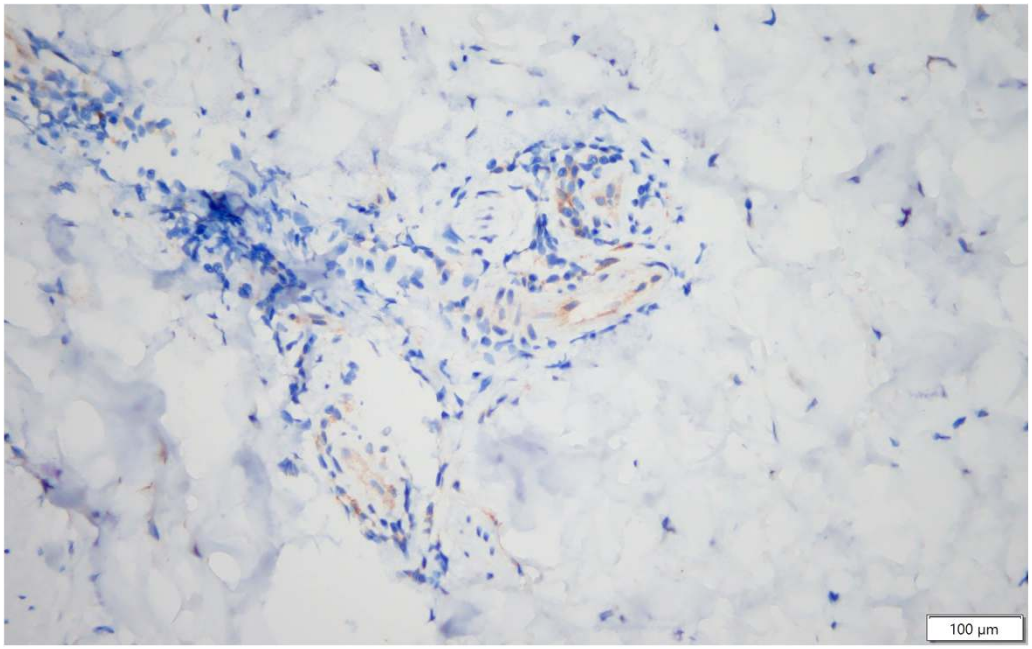
MxA



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DIAGNOSIS:
A. 4 Slides, 1 Block PAS-23-19991:
-C5b-9 MEDIATED MICROVASCULAR INJURY SYNDROME IN ASSOCIATION WITH UPREGULATION OF TYPE-I INTERFERON SIGNALING IN ENDOTHELIUM, MOST COMPATIBLE WITH A PERNIOTIC LIKE PRESENTATION OF A FORM FRUSTE VASCULAR INTERFERONOPATHY SYNDROME.

In addition, the clinical features of his compartment syndrome were reminiscent of systemic capillary leak syndrome, where upregulation of type I interferon signaling in the endothelium likely contributes to enhanced vasopermeability.[1]

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Additional testing revealed the patient has myotonic dystrophy type 2

Test(s) Requested

CNBP Gene / Myotonic Dystrophy, Type 2 (DM2)

Result: Positive

Gene	Mode of Inheritance	Variant	Zygosity	Classification
CNBP	Autosomal dominant	Repeat Number: >75 Repeat Number: 22	Heterozygous Heterozygous	Pathogenic Variant Normal

Reference Range

Classification	CCTG Repeat Size
Normal	26 or less
Intermediate	27-74
Positive	75 or greater

Interpretation

This individual harbors one expanded allele of greater than 75 CCTG repeats and one normal allele of less than 26 CCTG repeats, which is consistent with myotonic dystrophy type 2.

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Overview of Terms

Interferons are proteins produced by the immune system in response to pathogens like viruses.

Type I Interferons (IFN-α, IFN-β) are produced as part of the innate immune response, especially during viral infections:

- Plasmacytoid dendritic cells (pDCs)
- Fibroblasts
- Monocytes/macrophages

Interferonopathies are disorders where the interferon signaling pathway is dysregulated.

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Broad Overview of Mitochondrial Disorders

- Mitochondrial disorders broadly disrupts energy metabolism, redox balance, and cellular signaling — leading to oxidative stress and multi-organ dysfunction.
- Many different mitochondrial disorders, all can ultimately lead to mitochondrial membrane permeability and apoptosis.
- Mitochondrial DNA then accumulates within the cytoplasm of the cell, **which is a potent trigger of the cGAS-STING pathway.**

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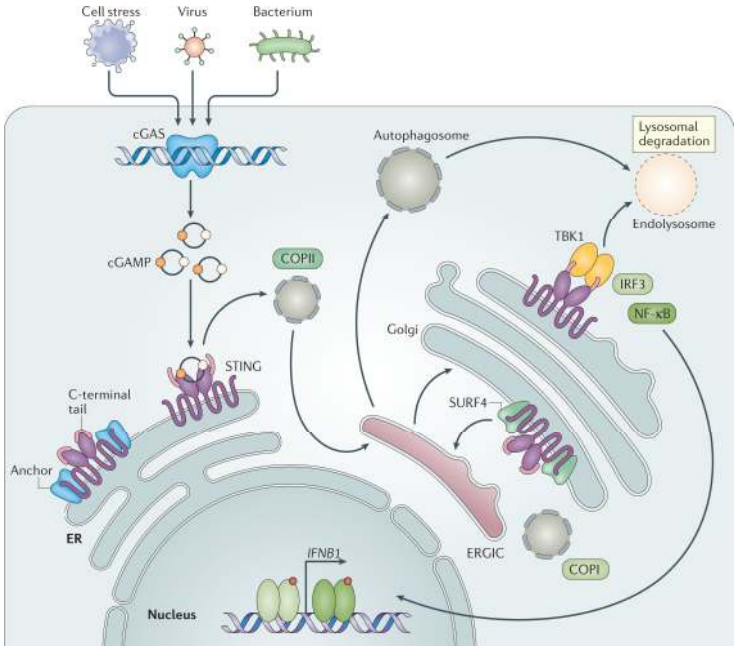
cGAS-STING pathway leads to upregulation of pro-inflammatory genes.[2]

Recognizes long segments of DNA in the cytoplasm

Produces cGAMP, which binds to STING

STING oligomerization → trafficking from ER to Golgi → IRF3 (interferon regulatory factor 3) translocation to nucleus → gene expression of type 1 interferons, ISGs, etc.



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Type I Interferons Directly and Indirectly Affect Endothelial Cells[3,4,5]

- Upregulation of JAK-STAT pathway in endothelial cells, which leads to increased expression of MHC class I molecules. This makes endothelial cells more susceptible to immune surveillance.
- Induces ICAM-1, VCAM-1, and E-selectin expression → promotes leukocyte adhesion and transmigration → release ROS/cytokines → local inflammation and endothelial injury.
- Upregulates complement components and coagulation factors via several direct and indirect pathways, which contribute to microvascular thrombosis and endothelial dysfunction.

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Interferonopathy Syndromes that Manifest in the Skin[6]

1. Kohlmeier Degos disease
2. Idiopathic perniosis
3. COVID19 perniosis
4. Aicardi Goutier syndrome perniosis
5. Dermatomyositis
6. Lupus erythematous

Among others

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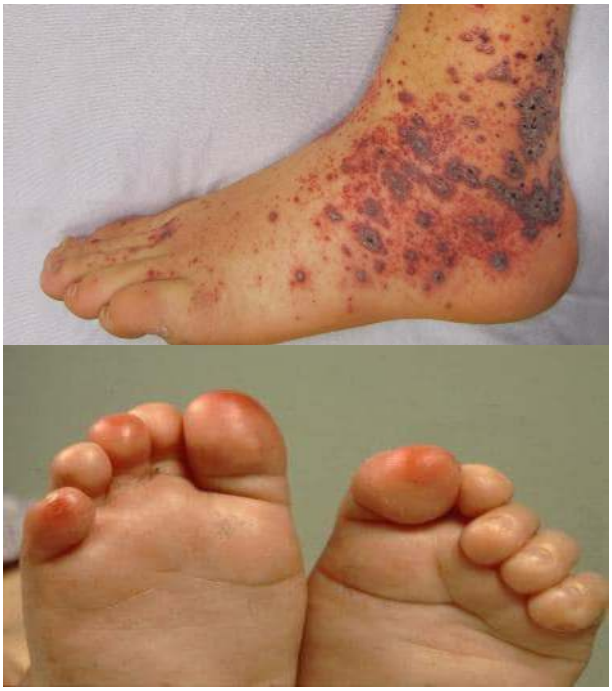
Interferonopathy Syndromes[6,7]

A common theme in these conditions is a lymphocytic vasculitis associated with upregulation of MXA staining in endothelium and microvascular deposition of complement

→ Type I interferon signaling can enhance the adaptive humoral immune response, generating antibodies that complex to antigen to evoke an Arthus type III reaction (case 1)

→ Target endothelium more directly, potentially contributing to the perniosis seen in case 2.



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Brief Summary

Mitochondrial dysfunction →

Mitochondrial DNA accumulates in cytoplasm of cell →

Increased Type I IFN production via the cGAS-STING pathway→

Endothelial activation (adhesion molecules, JAK-STAT) →

Immune cell recruitment →

Vascular permeability, inflammation and injury

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Conclusion

Patients with mitochondrial disorders are prone to several inflammatory disorders due to chronic overactivation of type I interferon signaling.

This represents an important bidirectional association: interferonopathies may reveal underlying mitochondrial dysfunction, and mitochondrial dysfunction may, in turn, manifest with interferonopathy syndromes.

Any case showing a lymphocytic vascular reaction with positive MXA staining should raise consideration regarding a primary interferonopathy syndrome.

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Citations

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Thank you

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