Waldenstrom and dermatology

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Objectives

- To understand disease related cutaneous manifestations of Waldenstrom's
- To understand treatment related cutaneous manifestations of Waldenstrom's
- To understand what to do with either disease or treatment related skin effects

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Quick overview of WM

- The IgM protein is the protein which is overproduced in WM
  - We test this through labs called quantitative immunoglobulins and the M-spike
- IgM is a large molecule and can infiltrate many things including the skin
- Because of the size of the molecule it can also cause other complications which can lead to skin disorders which we will discuss in further detail
- There are 3 classifications of WM (IgM MGUS, smoldering, and symptomatic)
- Various treatments that are necessary to treat *symptomatic WM* can also lead to skin/hair/nail changes

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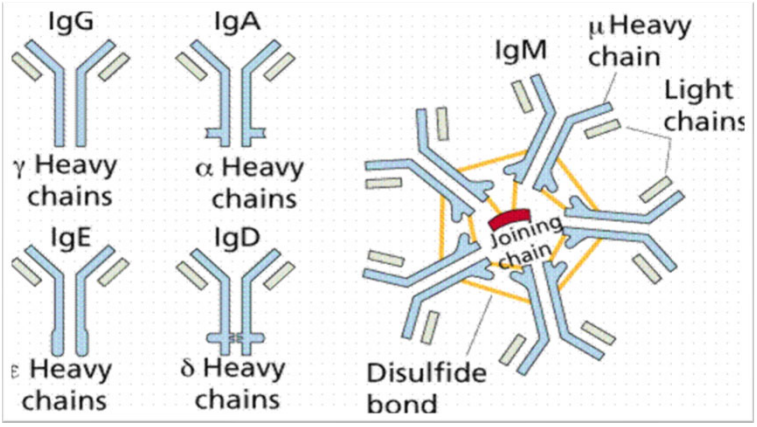
IgM molecule compared to others



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IgM levels

- The level of IgM and/or the percentage of LPL (WM) cells in the bone marrow varies tremendously between WM patients
- Some patients with very low IgM levels have lots of symptoms while others with very high levels may not have symptoms at all!

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Various Dermatologic Conditions

Treatment Related

- Brittle/cracking nails
- Corkscrew hair changes
- Skin infections
- Bruising/bleeding
- Psoriasis post Rituxan
- Neutrophilic dermatosis (Sweets syndrome) and neutrophilic eccrine hidradenitis

Disease Related (~5% patients w/ WM)

LPL cell infiltration

Hyperviscosity

Purpura

Raynaud's phenomenon

Livedo reticularis

Vasculitis

Chronic urticarial (Schnitzler's syndrome)

Seiter, K., Ponce, D. (2021).

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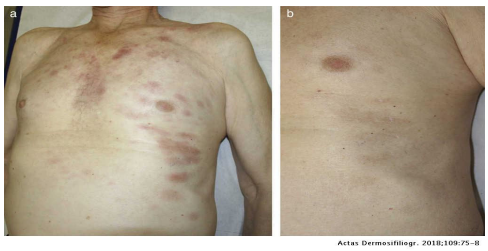
Disease Related

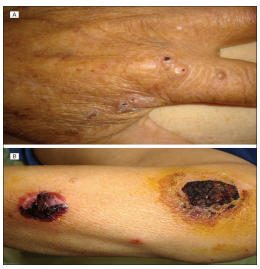
- Dermatologic manifestations with WM are a less common presenting symptom upon diagnosis with only about 5% of people having this.
- There is neoplastic causes meaning the skin is infiltrated with the LPL cells and non-neoplastic meaning it is caused from complications of the IgM paraprotein. We will discuss these in the upcoming slides.

Disease Related (cont)

- Rarely the lymphoplasmacytic cells can infiltrate the tissue
- The rash can range from reddish-brown to purple w/ plaque like texture
- When IgM infiltrates the skin it is called cutaneous macroglobulinosis or bullous disease



Actas Dermosifiliogr. 2018;109:75–8



Gressier L, Hotz C, Lelièvre J, et al

Hyperviscosity

- Hyperviscosity with WM is common and can cause complication (bleeding, edema, headaches)
- This is when the blood becomes thick/sludge like from excess proteins in the blood
- Because of bleeding risk use caution with brushing/flossing, blowing your nose
- The thicker blood can cause swelling in the legs (edema) which can cause the skin to blister or weep

Disease Related (cont)

Cryoglobulinemia causes some of the dermatologic conditions associated w/ WM

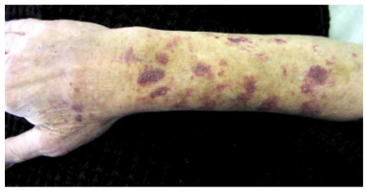
This is when blood proteins clump/precipitate in cold temps

Tested through a blood sample

Purpura- dark purple bruised looking spots on extremities

- This can cause pain at time is associated with vessel occlusion
- Can also be a result of hyperviscosity

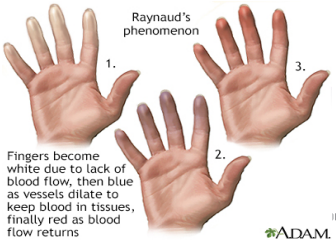
Lehman, J. 2010



Disease Related (cont)

Raynaud's phenomenon-

- occurs in cold temps from lack of blood flow
- Can cause acrocyanosis which is a blueish discoloration of the extremities, ears, and tip of nose
- Raynaud's occurs in cool or cold temperatures. This is when fingers become white, blue/purple from lack of blood flow, when blood flow return they become red.
- Keeping hands and/or feet warm with gloves, socks, hand or feet warmers to decrease pain and symptoms associated with Raynaud's



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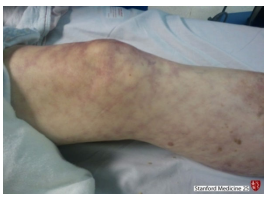
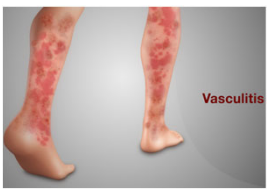
Disease Related (cont)

Cryoglobulinemia related conditions:

Livedo reticularis this web-like rash can be benign and transient or pathologic/more consistent or permanent

Vasculitis inflammation/narrowing or blockage of blood vessels





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Schnitzler Syndrome

- Urticarial eruptions- neutrophil (WBC) infiltrates
- Associated with IgM protein- more common with IgM Kappa vs IgM lambda
- Often have constellation of other symptoms (fever, bone or joint pain, swollen lymph nodes, and neuropathy)
- Rare and underdiagnosed
- Treatment is directed at treating WM and a medication called anakinra (immunosuppressant to target interleukin 1)

- Tania Jain, Chetan P. Offord, Robert A. Kyle, David Dingli. (2013)

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Neutrophilic dermatosis

- This is also called Sweets syndrome, named after Robert Douglas Sweet
- It is characterized by clinical, pathological, and lab findings
  - Clinical findings are fever, tender/red skin lesions, sometimes can affect areas outside the skin
  - Labs show increased neutrophils (a portion of the white blood cell)
  - Biopsy (pathology) of the lesions shows infiltration of mature neutrophils in the upper layer of the dermis
- Some people can have this without have a cancer diagnosis, but often times it is from an underlying malignancy
- Treatment requires systemic corticosteroids and sometimes topical steroid or injection into the skin lesion

- Al-Musalhi, B., Gerstein, W. (2016)

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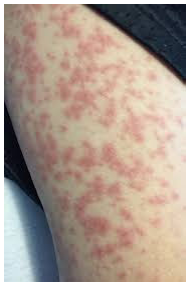
Neutrophilic eccrine hidradenitis

- This is a type of neutrophilic dermatosis
- This is a rash/skin eruption that is associated with chemotherapy most of the time
  - When chemotherapy stops, the rash generally improves.
- It affects the eccrine (sweat glands) that make up most of the body
- Can appear infectious and some people have accompanying fevers.
- Definitively diagnosed by skin biopsy
- It is self limiting, but can be treated with steroids (cautiously)



Crane JS, Krishnamurthy K. 2021

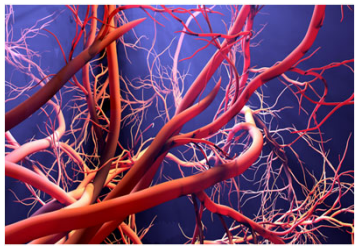
Mills, L. DO, Steinmetz-Rodriguez, C. DO, Folkes, A. DO, Shecter, R. DO, FAOCD

Changes to skin when WM is managed

- There can be changes to skin when WM is managed, these are mostly related to treatment side effects.
- Usually when specifically related to WM, meaning the skin lesion are infiltrated with IgM protein, they usually improve with treatment and can flare when disease progresses
- You want to have a biopsy to determine the exact cause, because it could be related to other skin conditions or amyloidosis (another plasma cell disorder)

Epidermal Growth Factor Receptor (EGFR)

- Epidermal growth factor is responsible for development/growth of new blood vessels
- Ibrutinib is intended to block BTK, but can also block the EGF receptor which can lead to unintended side effects
  - Rash
  - Bleeding/bruising
  - Infections (skin as well as systemic)
  - Atrial fibrillation
  - High blood pressure (hypertension)



Skin Infections

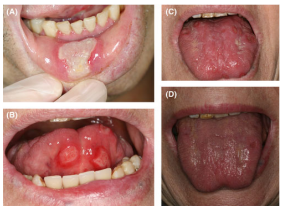
- Staphylococcus aureus- can be minor to very serious, requires oral antibiotics
  - Often times redness, pain, swelling of the skin, fevers
  - Called “cellulitis”
- Folliculitis- most minor type of staph infection at the base of a hair follicle, does not always require treatment, but can require an topical (applied to skin) antibiotic
- Panniculitis- inflammation of subcutaneous fat (adipose) tissue
  - May require corticosteroids and/or lower dose of ibrutinib

Sibaud, V., Beylot-Barry, M., Protin, C., Vigarios, E., Recher, C., & Ysebaert, L. (2020).

Fabbro SK, Smith SM, Dubovsky JA, Gru AA, Jones JA.

Skin Infections (cont)

- Herpes simplex and zoster (Shingles)
  - Prevention with medication or Shingrix vaccine
  - Post herpetic neuralgia can occur
- Aphthous ulcers/stomatitis
  - Generally not infectious or assoc. w/ neutropenia
  - Treat with corticosteroids (systemic and topical)
  - Pause ibrutinib and dose reduce



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Skin changes and what to do?

- Most common in the first year of treatment, but can occur at any time
- Cracked skin around fingers/toes, very brittle nails- Keep well moisturized
  - Mane and Tail lotion, Working hands lotion, don't use fragrance/alcohol based products
  - topical solutions such as hydrosoluble nail lacquer (Genadur) and polyureaurethane (Nuvail).
  - Biotin (2.5mg) -caution w/ thyroid
  - Keep clean to prevent infections
- Rash
- Hair changes- some thinning and corkscrew like texture

Bitar, C., Farooqui, M. Z., Valdez, J., Saba, N. S., Soto, S., Bray, A., Marti, G., Wiestner, A., & Cowen, E. W. (2016). Hair and Nail Changes During Long-term Therapy With Ibrutinib for Chronic Lymphocytic Leukemia. *JAMA dermatology*, *152*(6), 698–701. https://doi.org/10.1001/jamadermatol.2016.0225

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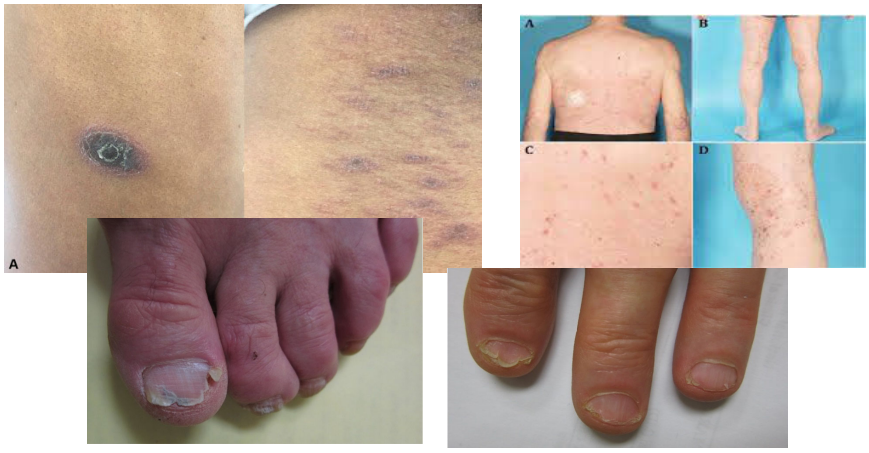
Skin/Nail changes



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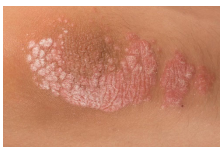
Skin changes (cont)

- Psoriasis post Rituxan-
  - Rare cases (1.04 in 1,000)- reported anytime during treatment
  - Generally resolves once Rituxan stops, sometimes requiring topical or systemic steroids
  - Cause is unknown, but could be from depletion of B-cell causing activation of T-cells, maybe from impaired response to infection, or from Rituxan induced auto-immune changes



  - Alahmari, H.S., Alhowaish, N.Y., Omair, M.A. (2019)

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Managing Toxicities

- Always discuss with your provider
- There are many interventions as we mentioned above and sometimes they require treatment breaks or dose reductions to minimize side effects

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Thank You

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