Association of Hidradenitis Suppurativa (HS) with myeloid cells dysplasias [myelodysplastic (MDS) or myeloproliferative syndromes (MPS)]: 4 cases

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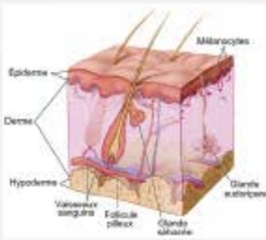
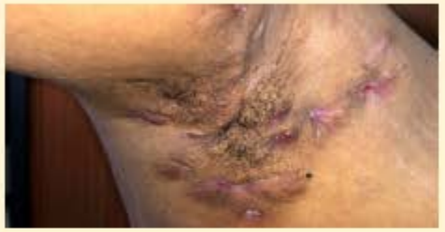


INTRODUCTION

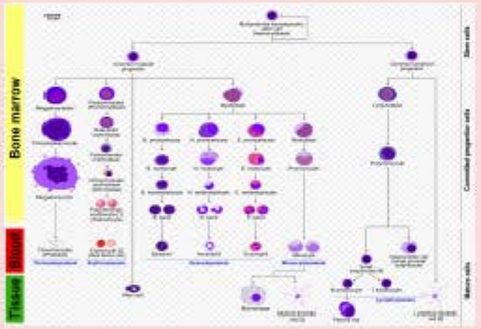


- In auto-inflammatory diseases (AID), there is now a known association with myeloid lineage diseases: in Vexas syndrome, polychondritis, or Sweet syndrome for example.
- The pathophysiology of such associations might relie on mutations in the ubiquitin pathway [1].
- HS belongs also to the spectrum of auto-inflammatory diseases: upregulation of interleukin 1β, interleukin-36, caspase-1, and NLRP3 and dysregulation of the Th17/Treg cell axis have been demonstrated, suggesting that autoinflammation is a key event in the pathophysiology of the disease [2].

METHODS/PROCEDURE

PATIENTS

- Notably, HS may be associated with other AID such as inflammatory bowel diseases or pyoderma gangrenosum, highlighting again the importance of autoinflammation in HS.
- We present 4 HS cases, associated with myeloid lineage diseases, as described now in other AID. This association is probably not fortuitous

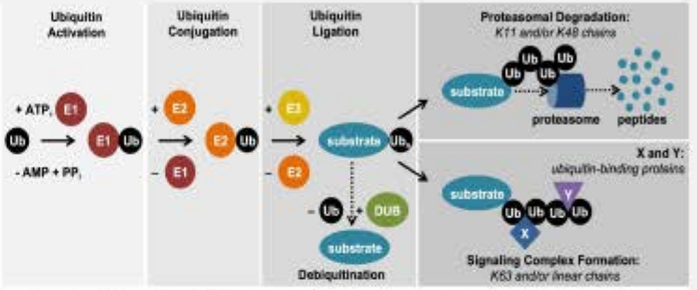


	Age	Type of hematologic disorder	Sex	Hurley stage	IHS4 at inclusion	Disease duration of hematological disease before HS (yrs)	Hematologic treatment
Patient 1	36	Myeloid chronic leukemia	♂	II	8	4,1	Imatinib
Patient 2	46	Myelofibrosis	♂	II	12	2,5	Ruxolitinib
Patient 3	38	Multilineage dysplasia	♂	II	11	3,7	Azacytidine
Patient 4	39	Multilineage dysplasia	♂	II	14	3,2	Azacytidine

- 4 patients were included in this short series, 2 men, 2 women.
- Mean age: 39 (36-46). All were classified as Hurley II. For all of them, the hematologic disease had begun before HS (3,6 years before in average).

- 2 myelodysplastic syndromes (MPS) (myeloid chronic leukemia and myelofibrosis); 2 MDS (multilineage dysplasias).
- Mean IHS4 at inclusion: 12 (8-14). Only 1 smoker.
- Treatments used for the underlying hematologic disease: ruxolitinib, azacytidine or imatinib

RESULTS

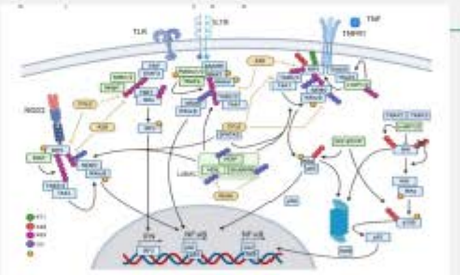


Ubiquitination is a multistep process that involves ubiquitin activation by E1 enzymes, ubiquitin conjugation to E2 enzymes, and ubiquitin ligation to the substrate protein via E3 enzymes. Ubiquitination can result in proteasomal degradation of the substrate or in recruitment of the substrate to multiprotein complexes, depending on the topology of the polyubiquitin chain linkages. X and Y indicate ubiquitin chain binding proteins.

EVOLUTION

- The antibiotics failed in all patients (doxycycline and association of clindamycin / levofloxacin), and they were all switched to adalimumab.
- Success in 3 patients with an 18-month treatment duration on average currently and mean IHS4 reached and maintained: 4.
- Failure in the other case, switched to secukinumab, with success (12 months treatment currently), IHS4 reached: 5.
- Good control of the underlying hematologic disease, with no interaction with the biologics.

Hypothesis: role of ubiquitination



Signaling mediated by TNFR1, IL-1R, TLR3/4, or NOD2 relies on complex ubiquitination involving multiple ubiquitin chains to activate inflammatory gene expression. Green indicates ubiquitin ligases and yellow deubiquitinase. Ubiquitin linkage types are indicated in the figure.

Auto-inflammation

- Autoinflammatory diseases are characterized by recurrent sterile inflammation with lack of high autoantibody titers or antigen-specific T lymphocytes. They are caused by a dysregulation of innate immunity and involve a series of cutaneous and multiorgan diseases.
- The cutaneous involvement in autoinflammation is usually marked by accumulation of neutrophils. Apart from the classic neutrophilic dermatoses, such as pyoderma gangrenosum (PG), Sweet's syndrome, palmoplantar pustulosis, and erythema elevatum et diutinum, other dermatoses, including HS, share similarly increased levels of proinflammatory chemokines and cytokines with autoinflammatory diseases.
- The majority of autoinflammatory disorders are characterized by overproduction of interleukin-1β (IL-1β), which triggers the release of tumor necrosis factor alpha (TNFα) and interferon gamma, being subsequently responsible for neutrophil recruitment and activation as well as evasion of apoptosis.

CONCLUSION

- HS is very complex and can be considered as an auto-inflammatory disease and might share some pathophysiological issues with other AID (Vexas, relapsing polychondritis,...), especially when associated with hematologic disorders.
- In these other AID, mutations in the ubiquitin genes have been discovered both in myeloid cells and in infiltrating cells in the dermis [1].
- The subsequent overexpression of the IFN pathway is supposed to play an important part in the pathogenesis. IFN should probably be avoided in these hematologic patients and JAK inhibitors preferred to treat both HS and the underlying hematologic disease.
- This is at our knowledge a rarely reported association in HS.
- The next step should be to search for the ubiquitin mutations in these particular patients, which could be added to the already known pro-inflammatory gene mutations (NOD2, LPIN2, NLRP3, NLRP12, PSMB8, MVK, IL1RN,...).

Acknowledgements:
To the Internal Medicine Department for the fruitful discussion about auto-inflammatory diseases

References:
(1) Beck, D.B. et al. Disorders of ubiquitylation: unchained inflammation. Nat Rev Rheumatol 18, 435–447 (2022)
(2) Nomura T. Hidradenitis Suppurativa as a Potential Subtype of Autoinflammatory Keratinization Disease. Front Immunol. 2020 May 20;11:847