Novel Germline FLT3 Y842C Mutation in Isolated Leukemia Cutis: A Case Report Highlighting Potential Genetic Predisposition to Myeloid Malignancies

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Introduction

- **Leukemia cutis is a manifestation of myeloid sarcoma, a rare extramedullary presentation of acute myeloid leukemia (AML) or related myeloid disorders, which can be challenging to diagnose and treat**
- **Germline predisposition to myeloid neoplasms is increasingly recognized**
- **Gene mutations associated with leukemogenesis in AML include FLT3 (ITD and TKD), NPM1, RUNX1, CEBPA, and KIT, driving abnormal proliferation, impaired differentiation, and survival of myeloid precursor cells**
- **Ongoing discoveries of new gene mutations are expanding our understanding of leukemogenesis, improving diagnostics, risk stratification, and targeted therapies**

Case Report

An 81-year-old male presented with raised, erythematous lesions involving the upper extremities, which rapidly progressed to his trunk and other areas, accompanied by over 10 lbs. of unintentional weight loss. Skin incisional biopsy of the left proximal radial dorsal forearm showed leukemic infiltration of blastoid cells to the dermis (**Fig 1**). IHC staining was positive for the following myeloid lineage markers: CD4, CD56, CD68, CD45, and muramidase (**Fig 2**). Additional immunostains showed the cells to be negative for the following: CD34, CD117, myeloperoxidase, CD123, TCL1, TdT, S100, CD1a, CD3, CD20, CD30, CD138, and EBER-ISH, confirming the diagnosis of leukemia cutis. Next generation sequencing (NGS) of the tissue revealed a FLT3 Y842C mutation with a VAF 96.4%, along with several other mutations (see Table 1). Surprisingly, bone marrow showed essentially normal trilineage hematopoiesis but NGS of bone marrow sample showed the same FLT3 mutation with 48.5% VAF, indicating a likely germline origin, which was subsequently confirmed by skin fibroblast testing.

Skin Biopsy: H&E and IHC

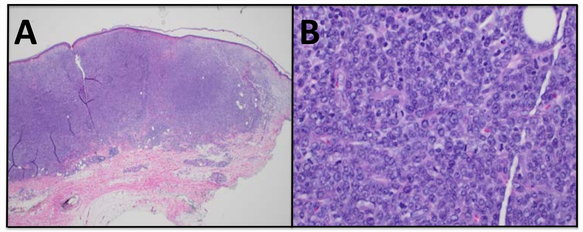

Figure 1: Diagnostic left forearm skin biopsy. A) Low power (10x) showing a dense dermal based infiltrate of atypical immature mononuclear cells ; B) High power (40X) highlighting blast morphology with dispersed chromatin, prominent nucleoli, and frequent mitoses.

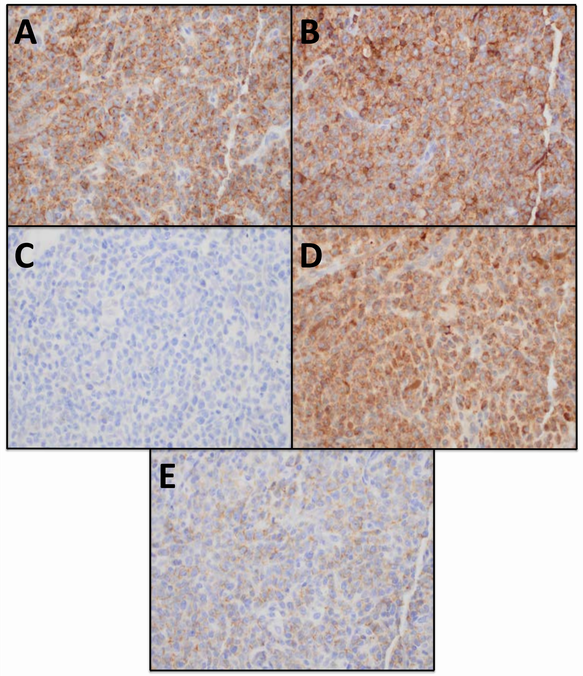

Figure 2: Immunohistochemical staining (all at 40x) for A) CD4; B) CD45; C) Myeloperoxidase; D) Muramidase/lysozyme; and E) CD56.

Genomic Comparison to Marrow

Genomic Changes	Leukemia Cutis	VAF	Bone Marrow	VAF
FLT3 Y842C	+	96.4%	+	48.5%
NPM1 W288fs*12	+	42.3%	-	N/A
U2AF1 R156H	+	45.3%	-	N/A
Loss of CDKN2A	+	N/A	N.D.*	N/A
Loss of CDKN2B	+	N/A	N.D	N/A

Table 1: Genomic testing for leukemia cutis tissue compared to bone marrow aspirate with associated variant allele frequency (VAF); N.D.* – Testing not done

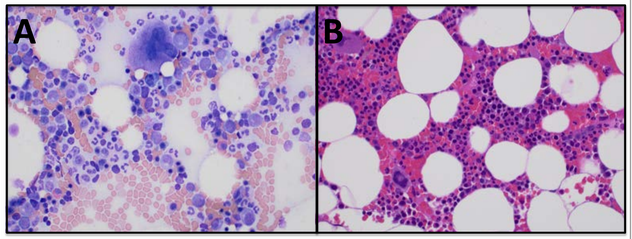

Figure 3: A) Bone marrow aspirate and B) bone marrow core biopsy without overt dysplasia or increase in blasts.

Case #	FLT3 variant	VAF	Additional variants	Diagnosis
1 (this patient)	Y842C	48.5%§		Isolated leukemia cutis
2	Y842C	49.4%*		Anemia
3	Y842C	55.1%		Acute promyelocytic leukemia
4	Y842C	41.9%	TET2 Y1649C (0.4763)	Myelodysplastic syndrome
5	N841_Y842insH	21.0%		Acute myeloid leukemia
6	Y842C	16.8%	PAX5 Y315Cfs*19 (0.131)	Mixed phenotype acute leukemia, B/Myeloid

Table 2: All pathogenic FLT3 codon Y842C variants identified at Moffitt Cancer Center obtained from either peripheral blood or bone marrow
§confirmed germline; *potentially germline

Conclusions

- **This case highlights a novel association between germline FLT3 activation loop mutation (Y842C) and leukemia cutis, suggesting a potential genetic predisposition to myeloid malignancy**
- **This mutation is known to be pathogenic; somatic mutation has been described in AML**
- **Only known report of germline FLT3 Y842C is in a case of B-lymphoblastic leukemia**
- **Germline testing for FLT3 Y842C may aid in identifying at-risk individuals, guiding early diagnosis and targeted management strategies**
- **Further studies are needed to understand the frequency and penetrance of this germline mutation in the formation of leukemia cutis, as well as other types of leukemia, and its impact on prognosis and therapy**

References

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