CASE REPORT
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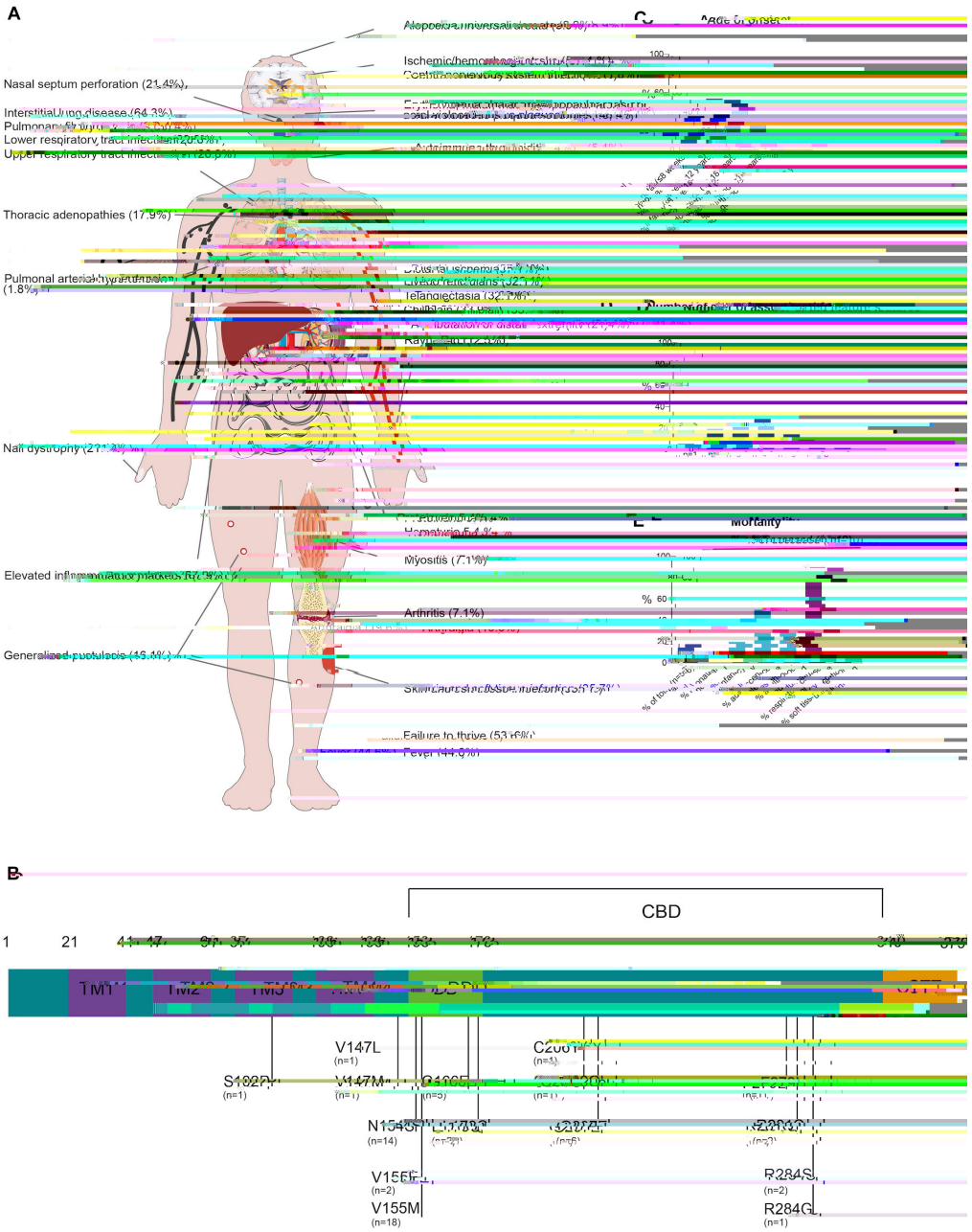

FIGURE 2 | Clinical and genetic synopsis of 56 SAVI patients. **(A)** Schematic representation of potential clinical presentations **(B)** Schematic representation of the STING protein, consisting of 4 transmembrane domains (TM1-4, blue), dimerization domain (DD, green), cGAMP binding domain (CBD, black bar) and C-terminal tail domain (CTT, orange). Gain-of-function mutations are indicated in black with number of cases reported underneath **(C)** Age of onset, *n* = 52 reported **(D)** Number of associated features, *n* = 56 reported **(E)** Mortality in SAVI patients, *n* = 56 reported.

system (1, 4). Clinically this commonly manifested as chilblains (33.9%), telangiectasia (32.1%), livedo reticularis (32.1%) and Raynaud phenomena (12.5%). Sometimes, more severe manifestations occurred such as acral ischemia necessitating amputations (21.4%) or ischemic/hemorrhagic stroke (5.4%) (1, 4). Cutaneous manifestations were common in SAVI, mostly with erythematous, malar, maculopapular rashes, and acral violaceous plaques (46.4%) with or without concomitant nail dystrophy (21.4%). Skin biopsy (performed in 37.5%) often

number of cases (30.4%), ILD progressed to pulmonary fibrosis. Other manifestations included intrathoracic lymphadenopathy (17.9%). Lung biopsies performed in 28.6% predominantly identified lymphocytic infiltrates surrounding alveoli and bronchioles (1–3).

STING-associated vasculopathy with onset in infancy patients are susceptible to soft tissue (35.7%) and respiratory tract (55.4%) infections, which can be related to their underlying vascular or pulmonary disease, as most patients had severe digital ischemia or underlying ILD or fibrosis. However, SAVI itself may carry an infectious susceptibility as a considerable percentage of patients had lymphopenia, leukopenia or impaired lymphocyte proliferation tests (1, 2, 6). Immunophenotyping in our proband also showed CD4 + T-cell, NK-cell lymphopenia and impaired T-cell proliferation (**Supplementary Table E1**). Arthralgia, myalgia and arthritis, mainly a□ecting the small joints, were noted in a 21.4% of patients. Renal manifestations are rare (7.1%). One patient of African-American ethnicity, presenting with skin vasculopathy and ILD, developed generalized edema due to nephrotic range proteinuria at the age of 14 months (4). Renal biopsy showed focal segmental glomerulosclerosis (4). Of note, this patient also carried two *APOL1* risk variants which are associated with this kidney disease. Another patient had mild renal involvement with microscopic hematuria and hypertension requiring treatment (7). However, no renal biopsy was performed. In our kindred, a pauci-immune intra- and extra-capillary glomerulonephritis with proteinuria and hematuria was observed.

Blood analysis across SAVI patients typically showed elevated C-reactive protein and sedimentation rate (67.9%), indicating systemic inflammation. Auto-immune serology was often determined and up to 62% of SAVI patients had positive autoantibodies (**Supplementary Figure E1**) mostly anti-nuclear antibody, followed by ANCA, anti-cardiolipin antibody, lupus anticoagulant, and anti-phospholipid antibody. These autoantibodies confound the diagnosis of SAVI, as some patients are initially classified as systemic lupus or ANCA-vasculitis (8) patients based on their presentation and serology.

Treatment with corticosteroids, disease-modifying anti-rheumatic drugs, anti-TNF, anti-CD20 and intravenous immunoglobulins in SAVI patients has had limited or no e□ect. Based on the pathophysiology, treatment with JAK-inhibitors was evaluated in a number of patients with, albeit with varying success (see **Supplementary Document E1**, available in the online repository). In the patient described here, treatment with rituximab, followed by glucocorticoids and azathioprine resulted in a remission of his ocular features and partial remission of renal disease up to 16 months of follow-up (**Supplementary Table E1**).

CONCLUSION

STING-associated vasculopathy with onset in infancy was initially identified in patients with early onset skin vasculopathy, ILD and prominent systemic features caused by *de novo* or familial gain-of-function mutations in STING. More recent reports have indicated a wider phenotypic spectrum including infectious, auto-immune, and even renal manifestations as in our case, with considerable variability between and within kindreds despite the presence of identical mutations. This clinical heterogeneity remains to be explained.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee of the University Hospitals of Leuven. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

FS, PD, BS, and RS initiated the work. FS, AB, MW, SV, IM, BS, YJC, SH-B, AL, and RS wrote the manuscript. PD provided the clinical care of the index patient. VC, YJC, and AC provided technical and/or diagnostic support. All authors contributed to the article and approved the submitted version.

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