EXTRAORDINARY CASE REPORT / BRIEF REPORT

Title: Histiocytoid Sweet syndrome presenting in two sisters with deficiency of deaminase type 2 (DADA2)

Running Title: Histiocytoid Sweet Syndrome in sisters with DADA2

Eugene Liat Hui Ong[1], Samantha Cooray[2], Paul Brogan[2], Eduardo Calonje[3]

[1]Dermatology Department, St George's Hospital, Blackshaw Rd, London, SW170QT.

Degrees: MB ChB, DipRCP Dermatopathology

[2]Rheumatology Department, Great Ormond Street, London WC1N 3JH

[3]Dermatopathology Department, St. John's Institute of Dermatology, St Thomas' Hospital, Westminster Bridge Road, London, SE17EH

Corresponding author: Eugene Ong

Email: eugene.ong@stgeorges.nhs.uk

[Word Count: (excluding abstract/references)]

Disclosures: None declared

Funding: None

Conflict of interest: None declared

Acknowledgements: None

Article Keywords: DADA2

ABSTRACT

INTRODUCTION

Deficiency of adenosine deaminase type 2 (DADA2) is an autosomal recessive monogenic autoinflammatory syndrome characterized by loss of function mutations in the ADA2 gene, formerly CECR1 (cat eye syndrome chromosome region 1) (Insert refs - Navon Elkan et al 2014 N J Med 370:10:921-931 and Zhou Q et al NN J Med 370:10:911-20). Mutations cause a deficiency or complete loss of ADA2 enzymatic activity. The ADA2 enzyme is primarily expressed and secreted by monocytes and macrophages and catalyses the conversion of adenosine to inosine in the blood (Insert original ref Zhou Q et al 2014 as above). The physiologic function of ADA2 is as yet poorly understood, but is thought to be an important

The earliest descriptions of DADA2 in 2014 were characterised by polyarteritis nodosa, systemic vasculitis and stroke, but the syndrome has since expanded to encompass a wide spectrum of vascular, haematologic and inflammatory manifestations, including bone marrow failure, neutropenia and immunodeficiency[2]. Growth factor regulating marrow development, cellular differentiation, and the balance between inflammatory M1 and anti-inflammatory M2 monocyte populations. Loss of function mutations can thus lead to marrow failure, autoinflammation, and vasculitis driven by inflammatory monocyte and endothelial interactions.

Here we report two sisters with similar presentations of histiocytoid Sweet syndrome, ultimately proven to have DADA2. To our knowledge, these are the first reported cases of such in the context of DADA2 deficiency syndrome.

Case Report #1

The younger 3-year-old sister presented with extensive, recurrent, non-symptomatic erythematous maculopapular rashes from 6 months of age. Individual erythematous areas lasted a few days before leaving purple purpuric areas. During flares she experienced fever, joint pains, mouth ulcers and complained of abdominal pain. She had a history of eczema and cow's milk protein allergy and Raynaud syndrome.

Blood markers for systemic inflammation were found to be consistently raised (Table 1) including CRP, ESR 30 and serum amyloid A (SAA). Other blood tests including full blood count, complement, ANA and ANCA were unremarkable. An ultrasound of the abdomen showed hepatosplenomegaly.

She underwent a 4mm punch biopsy of one of the urticated lesions of the leg. This showed a dense perivascular and interstitial dermal infiltrate of mononuclear histiocytoid cells with scant eosinophilic cytoplasm with only mild overlying epidermal spongiosis (Fig 1A-C).

These cells stained positive for CD33, CD163 and MPO, consistent with immature granulocytes (Fig 1D). This was in keeping with a diagnosis of histiocytoid sweet syndrome.

Case Report #2

The older 6-year-old sister presented similarly with widespread recurrent erythematous maculopapular rashes from 6 months old. Her rashes were not as florid or symptomatic as her sister. She also experienced recurrent mouth ulcers and joint pains. She had a history of previous thalamic and haemorrhagic strokes confirmed on brain MRI. Her systemic markers of inflammation were also raised (table 1) with otherwise normal full blood count and negative auto-antibodies. Her US abdomen showed hepatomegaly.

A 4mm punch biopsy on an area of raised urticated rash on her leg showed similar findings to that of her sister's: a dense dermal interstitial and perivascular infiltrate of immature granulocytes consistent with histiocytoid Sweet syndrome (Fig 2). Immunohistochemical findings were similarly positive for CD33, CD163 and MPO.

Given the presenting clinical features and history of stroke, both siblings underwent testing of serum ADA2 activity, which was found to be very low (0.24U/ml and 1.6U/ml, respectively; normal range 7-15U/ml). Subsequent genetic exome sequencing revealed heterozygous p.R169G/p.M309l heterozygous mutations in ADA2, which confirmed the diagnosis of DADA2 (Refs Nanthapisal S et al 2016, Arthritis Rheumatology 68(9):2314-22; Cooray et al. Rheumatology, Volume 60, Issue 9, September 2021, Pages 4373–4378, https://doi.org/10.1093/rheumatology/keaa837)

After initial treatment with long-term low dose oral prednisolone, both sisters received anti-TNF alpha therapy (Adalimumab 40mg every two weeks) which resolved their skin manifestations and blood inflammatory markers (Table 1). Both sisters have had recent disease flares coincident with the development of anti-drug antibodies against adalimumab, necessitating a switch to an alternative form of anti-TNF, etanercept, which is considered to be less immunogenic. Although systemic inflammation has improved, cutaneous flares with intercurrent infection have persisted, albeit much less severely than prior to anti-TNF. Fortunately, however, neither sibling has experienced and further strokes or other organ threatening vasculitic manifestation.

DISCUSSION

Histiocytoid Sweet syndrome is a rare variant of the inflammatory cutaneous disease Sweet syndrome. Clinically, patients present with widespread tender plaques often associated with fever. Histology it is characterised by immature myeloid cells in the upper dermis and marked papillary dermal oedema. Sweet syndrome has been associated with a wide range of conditions such as autoimmune diseases, inflammatory bowel disease and malignancy, and, most commonly, haematologic malignancies like acute myeloid leukaemia and myelodysplastic syndrome [Allegria-Landa; villareal].

To our knowledge, these are the first reported cases of histiocytoid Sweet syndrome in association with DADA2. Our patients did not have any other underlying malignancy or autoimmune disease that could account for her Sweet syndrome.

Over 80 different mutations leading to DADA2 have been reported (put ref here). In genotype-phenotype correlation studies, different mutations have been found to be more prevalent in particular populations and give rise to different disease manifestations and treatment responses. For instance p.R169Q mutations are most common in European populations and are associated with stroke whilst, p.G47R in Turkish populations and appear to have poorer prognosis and be more refractory to anti-TNF therapy [Lee et al]. Though poorly understood, cases with identical mutations, even within the same family, have been reported to experience different clinical manifestations [nanthapisal].

The cutaneous manifestations were very similar in these siblings; whilst the elder sibling had evidence of sub-clinical stroke on imaging, the younger sibling had not developed this at the time of initiating anti-TNF. Both, however, displayed typical features of autoinflammatory medium vessel vasculitis associated with mis-sense mutations and someresidual enzymatic activity, the commonest type of mutations in DADA2. Patients with more detrimental types of mutations (such as exonic deletions) and virtually absent ADA2 activity tend to produce more haematological manifestations like bone marrow failure and red cell aplasia, and less vasculitis [Lee]. Irrespective of that, the development of anti-drug antibodies and disease flare in these siblings emphasises how therapeutically precarious DADA2 has proven to be; gene therapy in the future will almost certainly alter the lifetime prognosis for this severe disease.

References

1. Zhou, Q., Yang, D., Ombrello, A.K., et al. 2014. Early-onset stroke and vasculopathy associated with mutations in ADA2. *New England Journal of Medicine*, *370*(10), pp.911-920.
2. Meyts, I. and Aksentijevich, I., 2018. Deficiency of adenosine deaminase 2 (DADA2): updates on the phenotype, genetics, pathogenesis, and treatment. *Journal of clinical immunology*, *38*(5), pp.569-578.
3. Van Montfrans JM, Hartman EA, Braun KP, Hennekam EA, Hak EA, Nederkoorn PJ, et al. Phenotypic variability in patients with ADA2 deficiency due to identical homozygous R169Q mutations. *Rheumatology (Oxford)* 2016;55(5):902–910
4. Genotype and functional correlates of disease phenotype in deficiency of adenosine deaminase 2 (DADA2). *Lee PY, Kellner ES, Huang Y, Furutani E, Huang Z, Bainter W, Alosaimi MF, Stafstrom K, Platt CD, Stauber T, Raz S, Tirosh I, Weiss A, Jordan MB, Krupski C, Eleftheriou D, Brogan P, Sobh A, Baz Z, Lefranc G, Irani C, Kilic SS, El-Owaidy R,*

Lokeshwar MR, Pimpale P, Khubchandani R, Chambers EP, Chou J, Geha RS, Nigrovic PA, Zhou Q. J Allergy Clin Immunol. 2020 Jun; 145(6):1664-1672.e10.

5. Deficiency of Adenosine Deaminase Type 2: A Description of Phenotype and Genotype in Fifteen Cases.

6. *Nanthapisal S, Murphy C, Omoyinmi E, Hong Y, Standing A, Berg S, Ekelund M, Jolles S, Harper L, Youngstein T, Gilmour K, Klein NJ, Eleftheriou D, Brogan PA. Arthritis Rheumatol. 2016 Sep; 68(9):2314-22.*

7. *Alegría-Landa V, Rodríguez-Pinilla SM, Santos-Briz A, et al. Clinicopathologic, Immunohistochemical, and Molecular Features of Histiocytoid Sweet Syndrome. JAMA Dermatol. 2017;153(7):651–659. doi:10.1001/jamadermatol.2016.6092*

8. *Villarreal-Villarreal CD, Ocampo-Candiani J, Villarreal-Martínez A. Sweet syndrome: a review and update. Actas Dermosifiliogr. 2016;107(5):369-378.*

Blood marker	Pre-Anti-TNF	Post- Anti-TNF	Pre-Anti-TNF	Post- Anti-TNF
CRP (mg/L) Normal < 20	16	<5	7	6
ESR (mm/Hr)	30	14	30	15
Neutrophils (*10^9/L) Normal 1-8.5	3.29	3.16	2.7	6.86
Lymphocytes (*10^9/L) Normal 3.0-13.5	2.66	4.26	8.63	6.32
AA amyloid (mg/L) Normal 20-50	86.3	16.7	83.7	<3.5

Table 1: inflammatory blood markers before and after Adalimumab

9.

Figure 1A

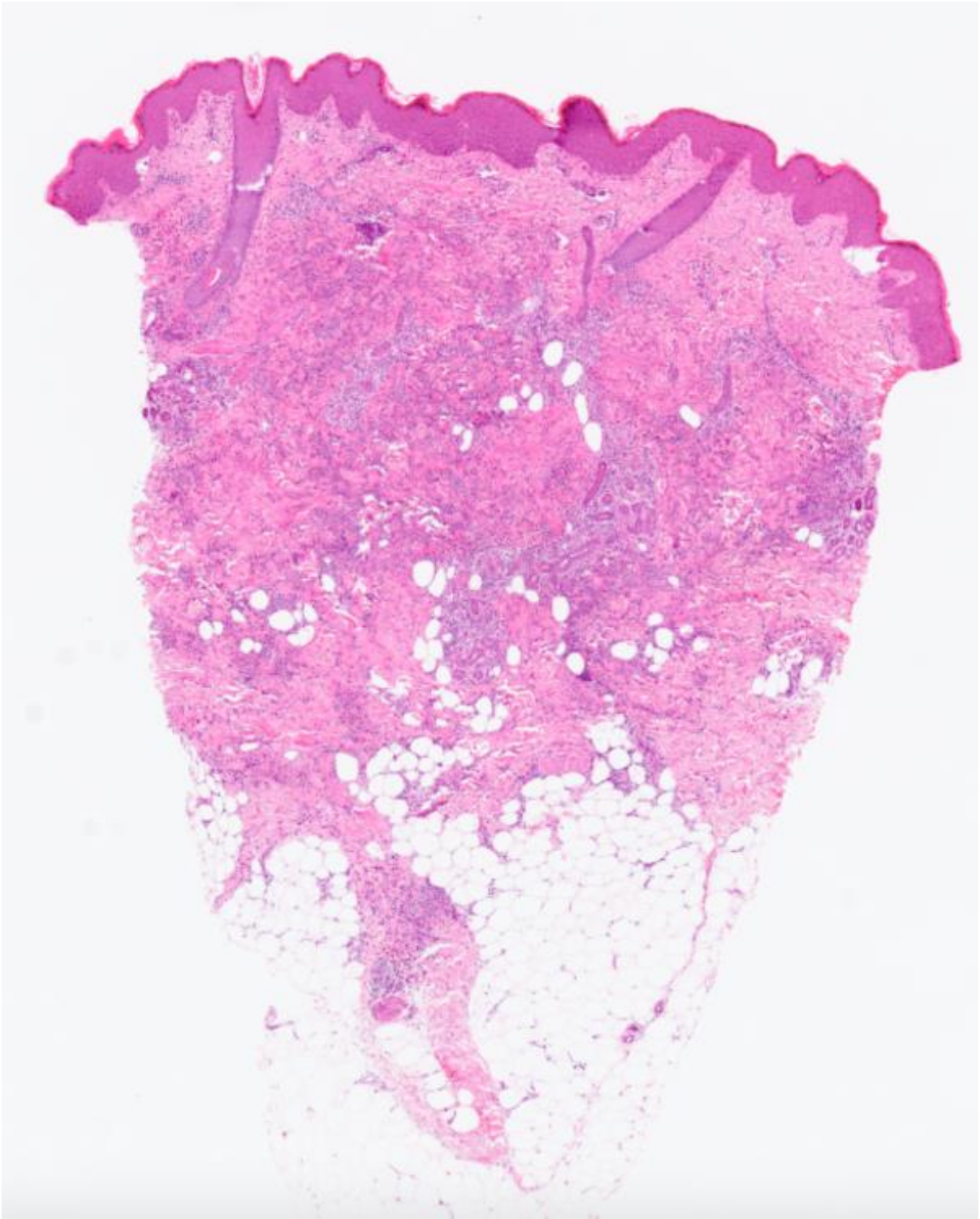


Figure 1B

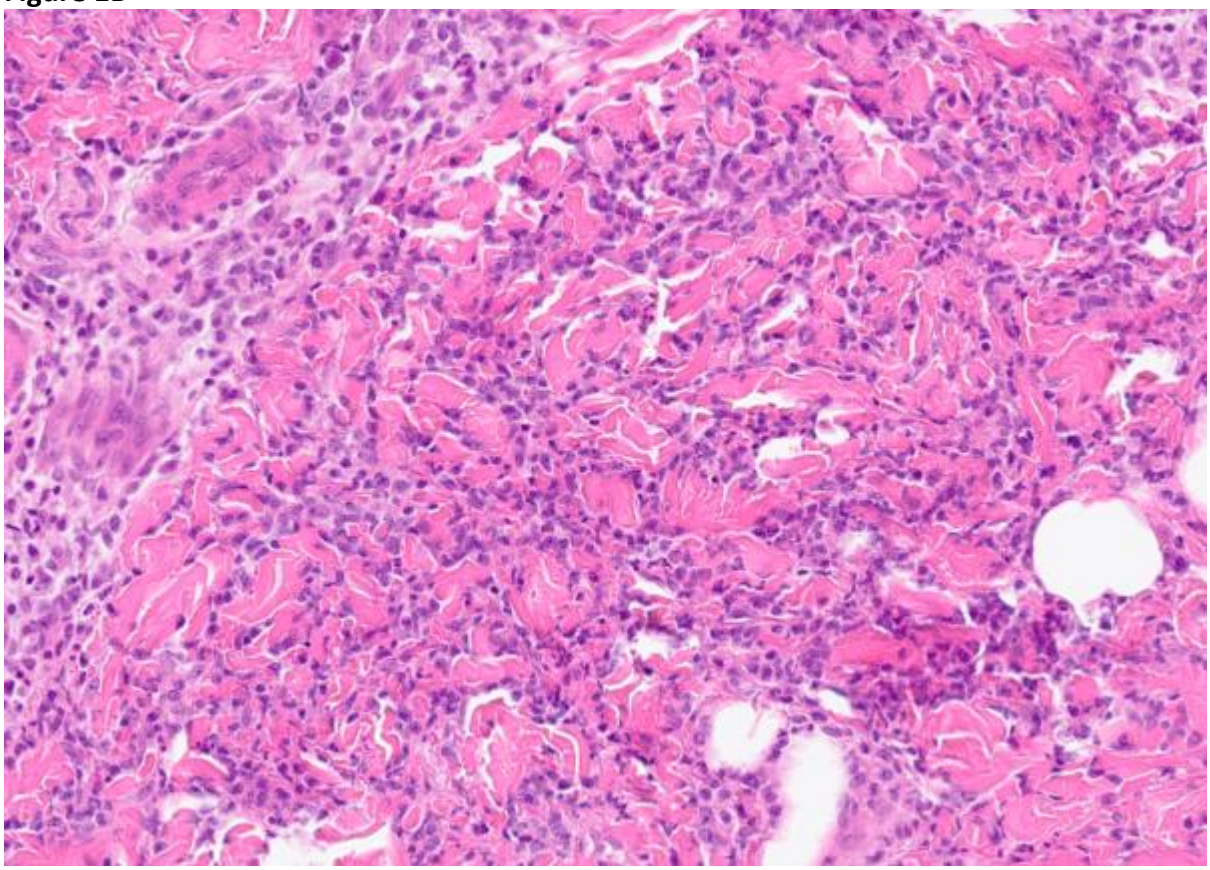


Figure 1C

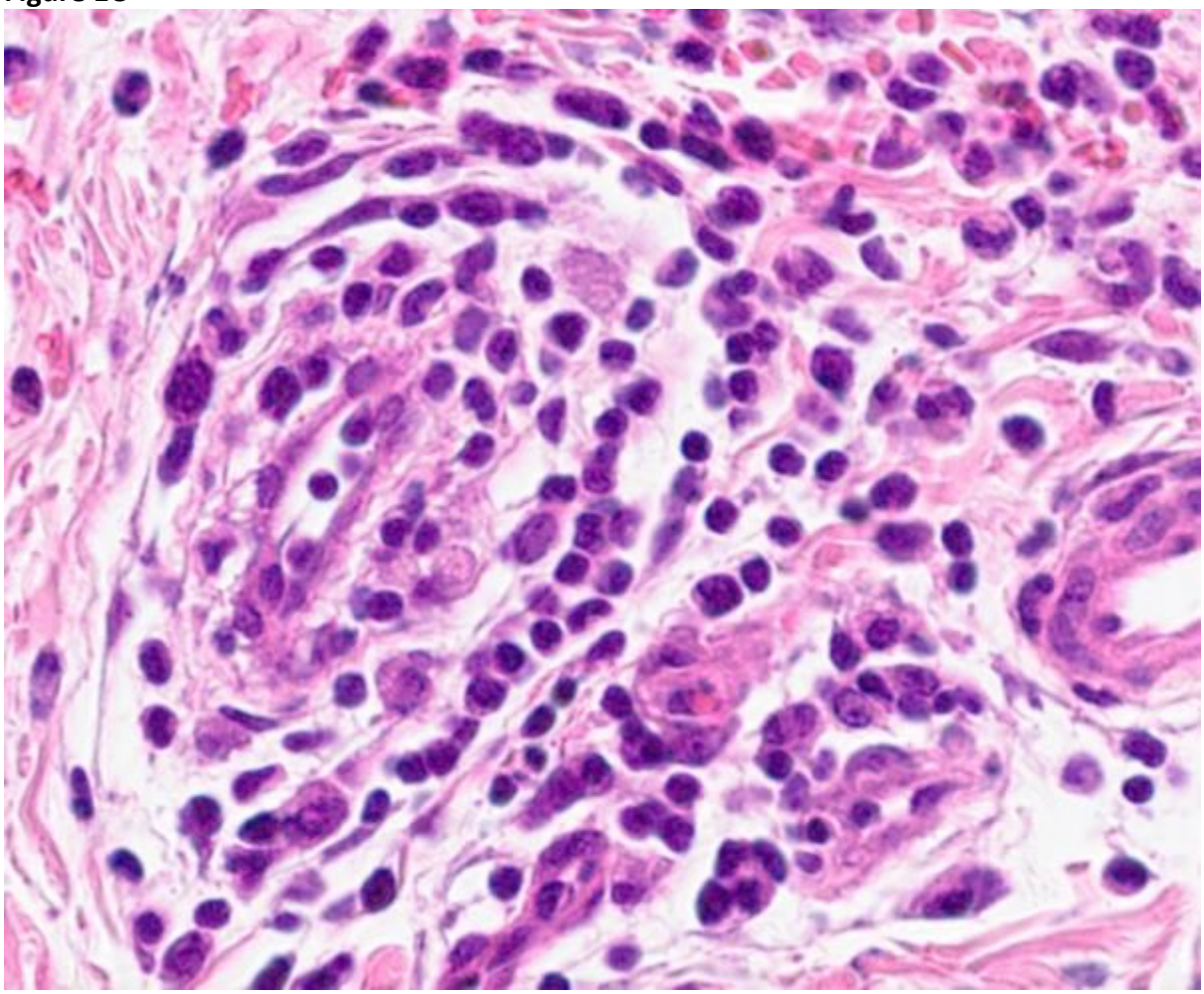


Figure 1D

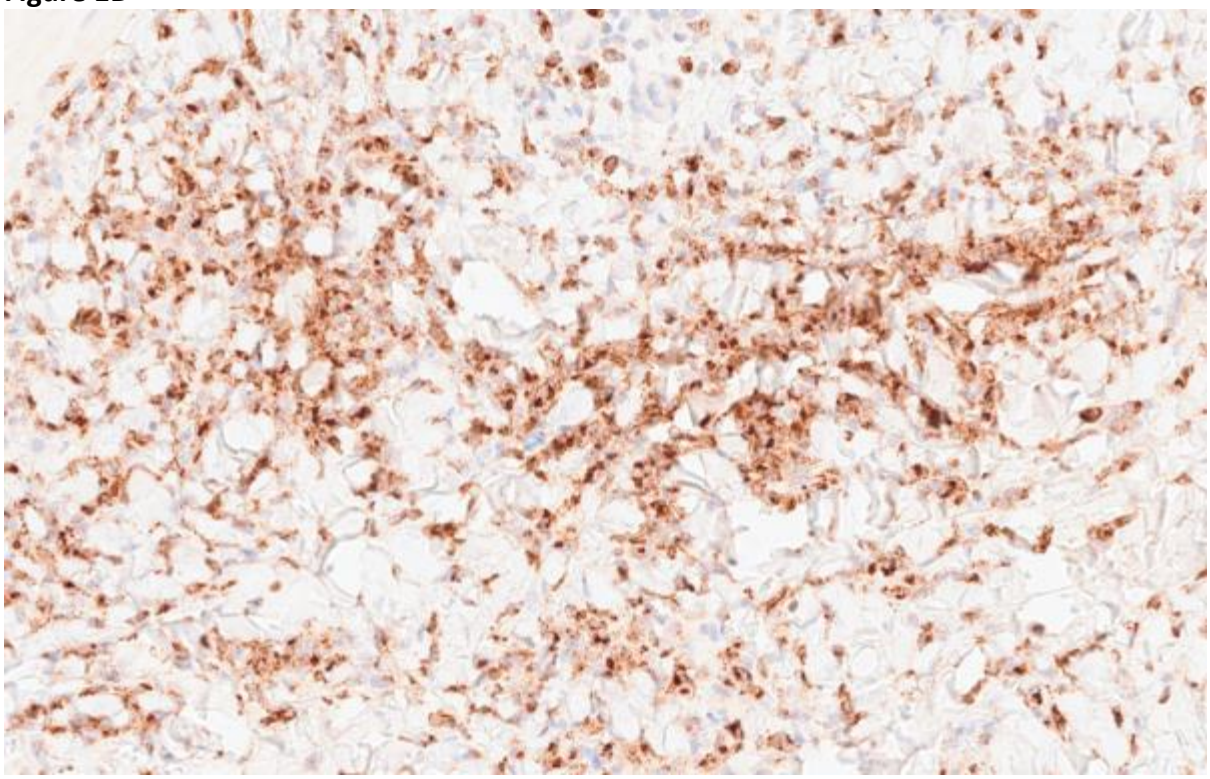


Fig 2A

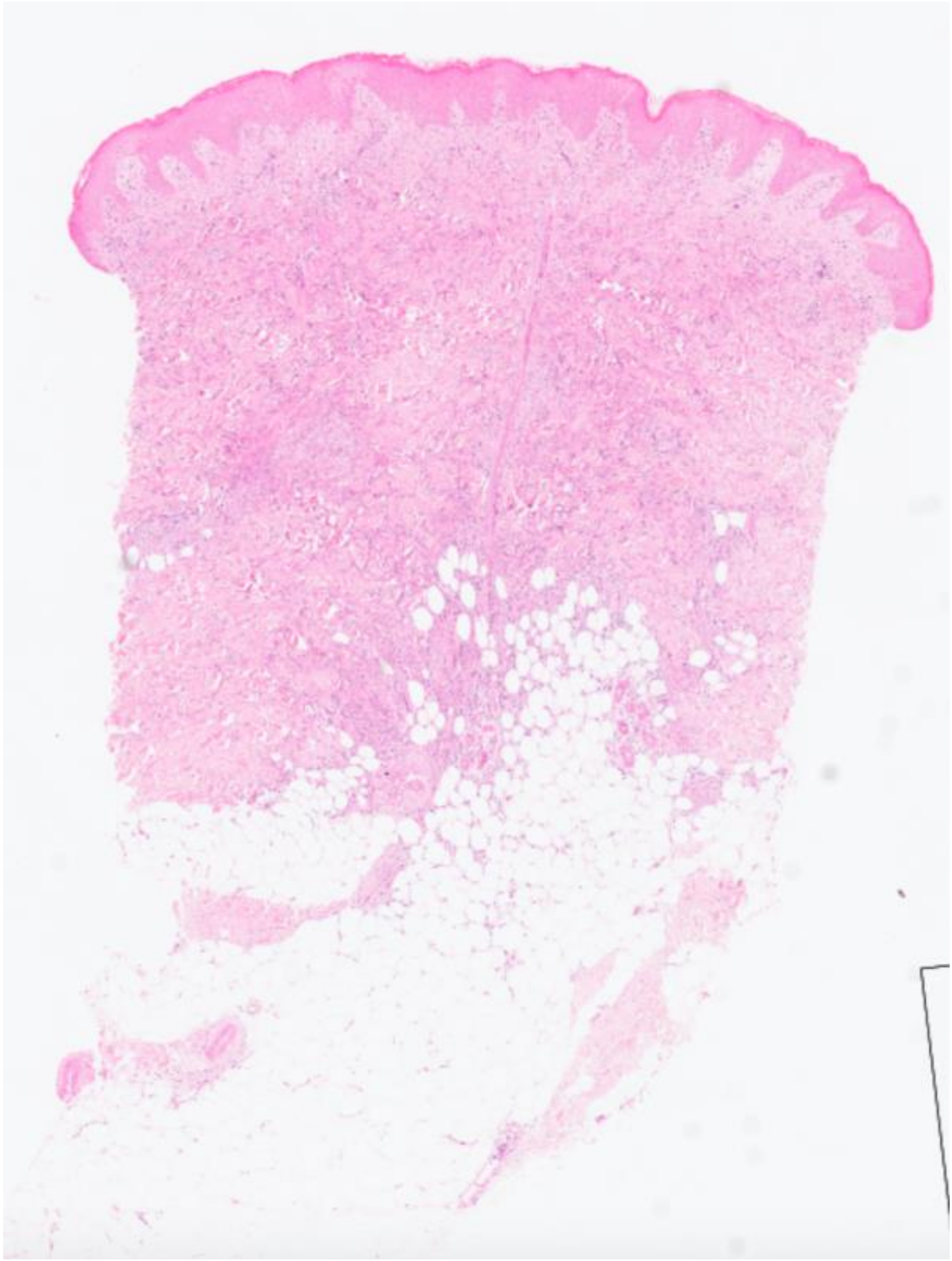


Fig 2B

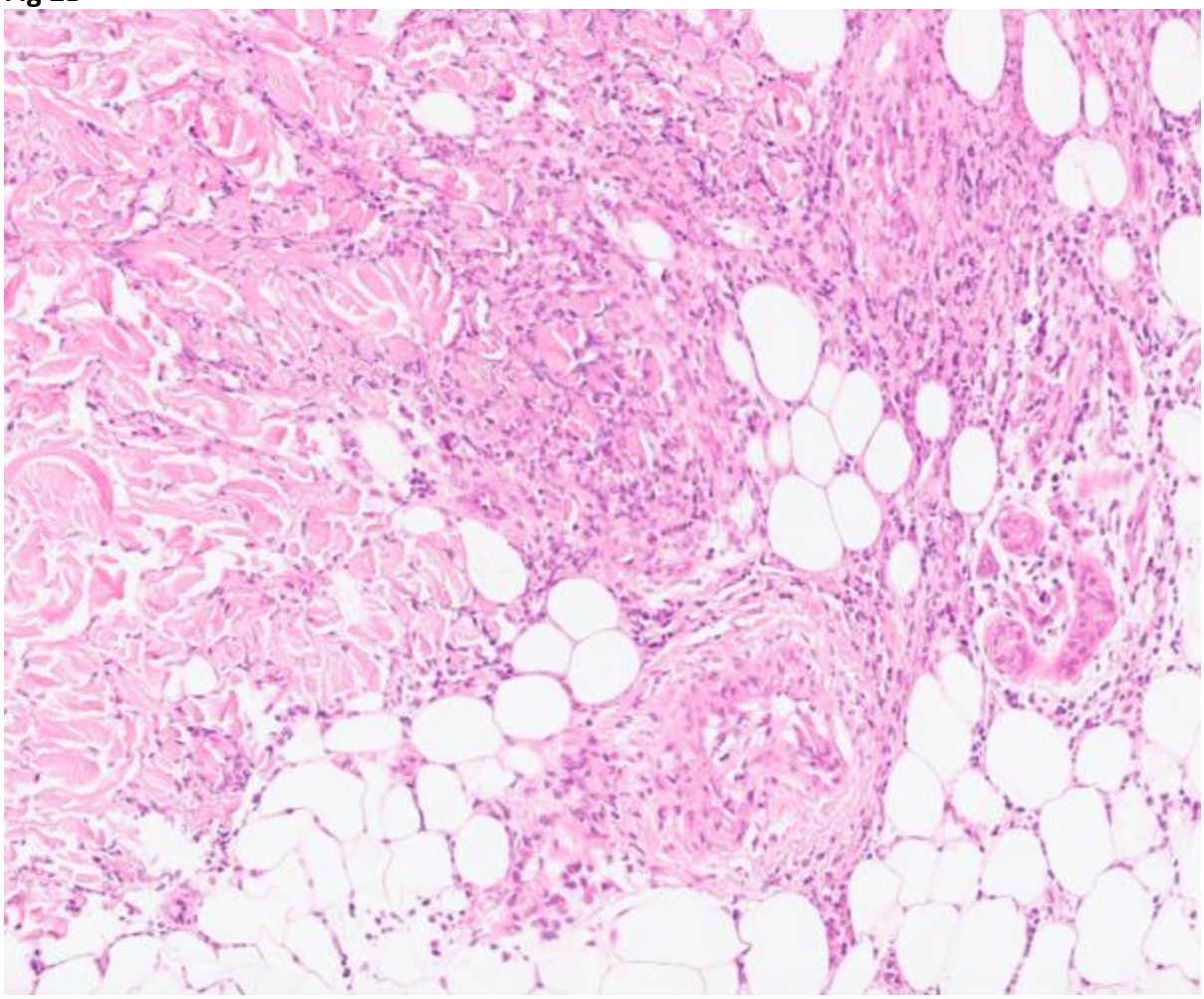


Fig 2C

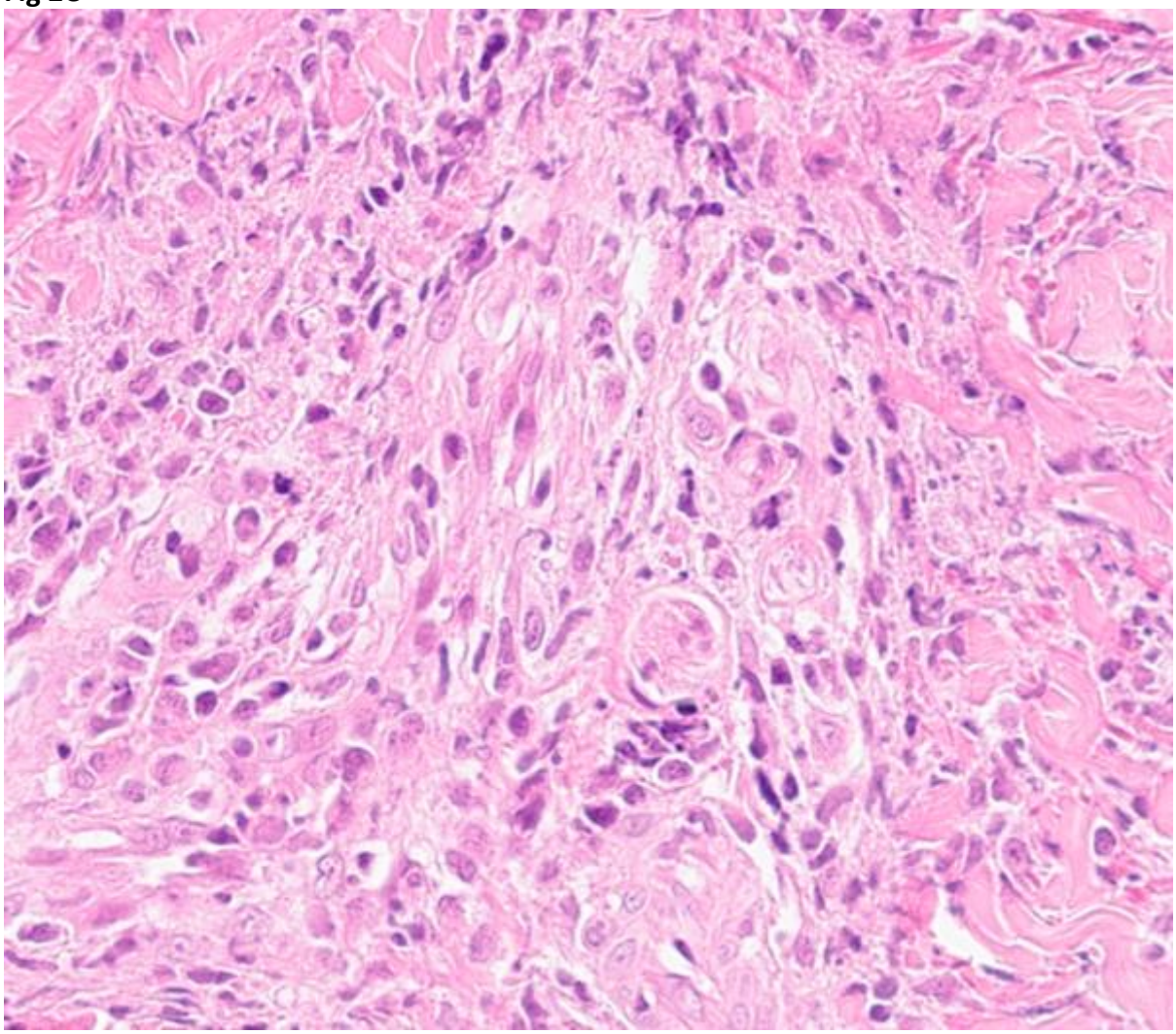
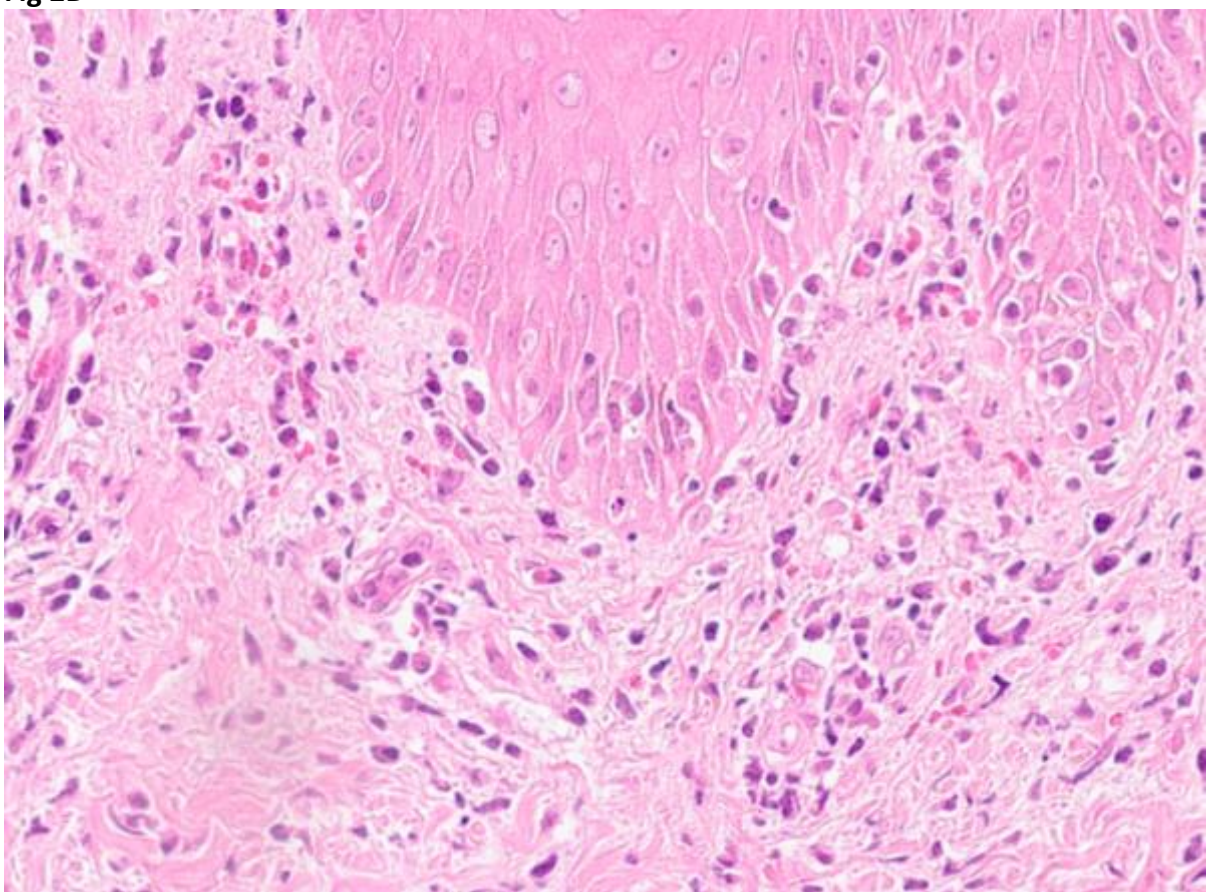


Fig 2D



Alternate: