Megaloblastic Pancytopenia Secondary to Vitamin B12 Deficiency: Clinical Spectrum, Diagnostic Clues, and Outcomes — A Case Series of 11 Patients

Siddharth Sahai[1], Deepak Sharma[2], Monty Bansal[3], Mayank Chandrakar[4] , Manav Gandhi[5]

[1]*Department of General Medicine, [Junior Resident], [Sharda School of Medical Sciences and Research]*
[2]*Department of General Medicine, [Professor and Head], [Sharda School of Medical Sciences and Research]*
[3]*Department of General Medicine, [Junior Resident], [Sharda School of Medical Sciences and Research]*
[4]*Department of General Medicine, [Junior Resident], [Sharda School of Medical Sciences and Research]*

[5]*Department of General Medicine, [Junior Resident], [Sharda School of Medical Sciences and Research]*

Corresponding author:
Dr. Siddharth Sahai
Department of General Medicine, Sharda School of Medical Sciences and Research, Greater Noida, Uttar Pradesh, India , PIN- 201310
E-mail: drsiddharthsahai9@gmail.com

Abstract

Background

Vitamin B12 (cobalamin) deficiency is a common, treatable nutritional disorder whose haematological expression ranges from mild macrocytic anaemia to florid pancytopenia that can mimic primary bone marrow failure or haematological malignancy. Because red-cell indices and peripheral smear morphology can be confounded by coexisting iron deficiency, the diagnosis is frequently delayed.

Cases/Methods

We retrospectively describe 11 patients (6 women, 5 men; age range 19–55 years) admitted to the Department of General Medicine with fatigue and generalised weakness, in whom evaluation revealed pancytopenia with markedly elevated mean corpuscular volume (MCV 118–136 fL). Haematological malignancy, aplastic anaemia, hypersplenism, and infectious or autoimmune causes of pancytopenia were excluded clinically and by laboratory work-up. Serum vitamin B12 assay and peripheral smear morphology were used to establish the diagnosis.

Results

All 11 patients had severe cobalamin deficiency (serum B12 132–200 pg/mL; mean, 172 pg/mL) with megaloblastic peripheral smear features—macro-ovalocytes, anisopoikilocytosis, and hypersegmented neutrophils—and four patients had clinically evident cutaneous knuckle or facial hyperpigmentation. All patients received parenteral vitamin B12 replacement. Nine of 11 patients had documented symptomatic improvement before discharge, and repeat B12 levels rose to 900–1000 pg/mL in most patients. Eight patients available for outpatient follow-up at four weeks showed sustained haematological recovery with reticulocytosis and required no re-hospitalisation.

Conclusion

Vitamin B12 deficiency is an important and fully reversible cause of pancytopenia that can be mistaken for more sinister bone-marrow disorders. A high index of suspicion—particularly when macrocytosis coexists with multilineage cytopenia, or when iron deficiency partially masks the classical macrocytic picture—allows early diagnosis, avoids unnecessary invasive investigations, and ensures prompt, inexpensive, and effective treatment.

Keywords: Vitamin B12 deficiency; Pancytopenia; Megaloblastic anaemia; Mean corpuscular volume; Cobalamin; Case series

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1. Introduction

Vitamin B12 (cobalamin) is a water-soluble vitamin obtained almost exclusively from animal-source foods and is essential for DNA synthesis, erythroid maturation, and myelin formation [1]. Deficiency of this micronutrient produces a clinical spectrum that extends well beyond the classical triad of anaemia, glossitis, and paraesthesia, and includes neuropsychiatric disturbance, subacute combined degeneration of the spinal cord, and, less widely appreciated, multilineage cytopenia [1–3].

Pancytopenia—simultaneous reduction in haemoglobin, total leukocyte count, and platelet count—is conventionally regarded as a "red-flag" finding that prompts evaluation for bone marrow failure syndromes, infiltrative or malignant marrow disorders, hypersplenism, and infections such as malaria, leishmaniasis, and HIV [4]. Bone marrow aspiration and biopsy are frequently undertaken as the next investigative step. However, multiple Indian series have consistently identified megaloblastic anaemia secondary to cobalamin or folate deficiency as among the most common causes of pancytopenia in this population, often rivalling or outnumbering aplastic anaemia and haematological malignancy [5–9].

Cobalamin deficiency is particularly prevalent on the Indian subcontinent because of the widespread practice of vegetarianism, limited dietary diversity, and a high background prevalence of chronic gastrointestinal and parasitic disorders that impair B12 absorption [10–14]. Reported prevalence estimates of subclinical or overt deficiency among Indian adults range from approximately 30% to over 70% in vegetarian cohorts [11,14].

A key diagnostic pitfall is the frequent coexistence of iron deficiency, which produces microcytic red cells that can numerically offset, or "mask", the macrocytosis that would otherwise be the principal clue to underlying cobalamin deficiency, yielding a normal or even low mean corpuscular volume (MCV) despite severe megaloblastic erythropoiesis [15–17]. This dimorphic picture can mislead clinicians into treating presumed iron-deficiency anaemia alone, allowing the B12 deficiency—and its haematological and neurological consequences—to progress unchecked.

We report a case series of 11 patients who presented to our General Medicine outpatient department with non-specific fatigue and weakness and were ultimately found to have severe vitamin B12 deficiency manifesting as pancytopenia with markedly elevated MCV. We describe the clinical, haematological, and dermatological features of this cohort and their response to parenteral cobalamin replacement, with the aim of reinforcing awareness of this common, inexpensive, and entirely reversible cause of multilineage cytopenia.

2. Materials and Methods

2.1 Study design and setting

This is a cross sectional, descriptive case series of patients evaluated in the Department of General Medicine, Sharda School Of Medical Sciences and Research, Uttar Pradesh , India, between January , 2025 and June, 2026.

2.2 Case ascertainment

Consecutive patients presenting to the outpatient department with fatigue and generalised weakness who, on initial complete blood count, were found to have pancytopenia (haemoglobin <11 g/dL, total leukocyte count <4000/cumm, and platelet count <1,50,000/mm3) together with a markedly elevated MCV (>100 fL) were admitted for further evaluation. Eleven such patients in whom severe vitamin B12 deficiency was subsequently confirmed as the cause of pancytopenia, after exclusion of alternative aetiologies, were included in this series.

2.3 Clinical and laboratory evaluation

All patients underwent a detailed history (dietary pattern, gastrointestinal symptoms, drug history, and, where applicable, menstrual history) and physical examination, with particular attention to pallor, glossitis, icterus, lymphadenopathy, hepatosplenomegaly, and cutaneous pigmentary changes. Baseline investigations included complete blood count with red-cell indices, peripheral blood smear examination, reticulocyte count, serum vitamin B12 and folate assay, serum ferritin/iron studies, renal and liver function tests, lactate dehydrogenase, and viral serology (HIV, hepatitis B and C). Additional investigations—including bone marrow aspiration, abdominal ultrasonography, autoimmune work-up, and peripheral smear examination for malarial parasites—were performed where clinically indicated to exclude alternative or coexisting causes of pancytopenia such as aplastic anaemia, haematological malignancy, hypersplenism, and infectious causes. Patients in whom an alternative or additional diagnosis was considered the dominant cause of pancytopenia were not included in this series.

2.4 Diagnostic criteria

A diagnosis of vitamin B12 deficiency–induced pancytopenia was made in the presence of (i) pancytopenia, (ii) macrocytosis, or megaloblastic morphology on peripheral smear even when the MCV was not markedly elevated, (iii) a low serum vitamin B12 level, and (iv) exclusion of other identifiable causes of pancytopenia.

2.5 Treatment protocol

All patients received parenteral vitamin B12 supplementation (injection hydroxocobalamin) as per standard institutional protocol, along with correction of any coexisting iron or other micronutrient deficiency where indicated, and supportive nutritional counselling.

2.6 Statistical analysis

Given the descriptive nature of this case series, data are presented as ranges, means, or proportions, as appropriate, without formal inferential statistical testing.

2.7 Ethical considerations

This case series was reviewed and approved by the Institutional Ethics Committee of [Name of Institution] (Approval No. [IEC/XXX/20XX], dated [date]). Written informed consent was obtained from all patients for publication of their clinical, laboratory, and photographic data, including the de-identified photographs reproduced in this article. The study was conducted in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments.

3. Results

3.1 Demographic and clinical profile

The series comprised 11 patients (6 women and 5 men) aged 19 to 55 years (mean age, 34 years). All patients presented with fatigue and generalised weakness of variable duration; easy fatigability and exertional intolerance were near-universal accompanying complaints. None of the patients reported overt gastrointestinal bleeding, jaundice, or fever at presentation, and physical examination was notable principally for pallor; four patients (patients A, C, D, and J) had clinically apparent cutaneous hyperpigmentation, predominantly over the knuckles and dorsa of the hands, and one patient (patient J) additionally had facial hyperpigmentation.

3.2 Haematological parameters

All 11 patients fulfilled criteria for pancytopenia at presentation. Haemoglobin ranged from 5.8 to 10.6 g/dL (mean, 8.5 g/dL), total leukocyte count from 2,950 to 4,100/cumm, and platelet count from 58,000 to 99,000/mm3. The MCV was markedly elevated in every patient, ranging from 118 to 136 fL (mean, 128 fL), consistent with megaloblastic erythropoiesis. Serum vitamin B12 levels were uniformly low, ranging from 132 to 200 pg/mL (mean, 172 pg/mL). The complete haematological and biochemical profile of all 11 patients is summarised in Table 1.

Table 1 Demographic, haematological, and biochemical profile of the 11 patients at presentation

Patient	Age (years)	Sex	Hb (g/dL)	TLC (/cumm)	Platelet (/mm3)	MCV (fL)	Serum B12 (pg/mL)
A	19	Male	5.8	3050	60,000	134.0	159
B	44	Female	9.5	3650	73,000	125.0	178
C	36	Male	8.7	3700	68,000	129.0	169
D	29	Female	10.6	4100	99,000	118.0	200
E	55	Female	7.3	3200	78,000	131.0	164
F	39	Male	10.3	3900	92,000	121.0	195
G	41	Male	8.4	3400	71,000	128.0	172
H	27	Male	7.7	2950	64,000	133.0	148
I	23	Female	7.0	3100	58,000	136.0	132
J	31	Female	8.3	3600	76,000	127.0	181
K	28	Female	9.8	4000	85,000	122.0	190

Hb haemoglobin, TLC total leukocyte count, MCV mean corpuscular volume

3.3 Peripheral blood smear findings

Peripheral blood smear examination in this cohort showed features typical of megaloblastic haematopoiesis, including macro-ovalocytosis, marked anisopoikilocytosis, dimorphic red-cell populations, occasional circulating nucleated red blood cells, and hypersegmented neutrophils (defined as neutrophils with five or more nuclear lobes). Representative smear findings from three patients are illustrated in Fig. 1: the smear from patient A demonstrated macrocytic, dimorphic anaemia with nucleated red blood cells (Fig. 1a); the smear from patient J showed numerous macro-ovalocytes with hypersegmented neutrophils (Fig. 1b); and the smear from patient D revealed a dimorphic red-cell population with marked anisopoikilocytosis (Fig. 1c), a finding consistent with coexisting iron deficiency partially masking the underlying megaloblastic process.

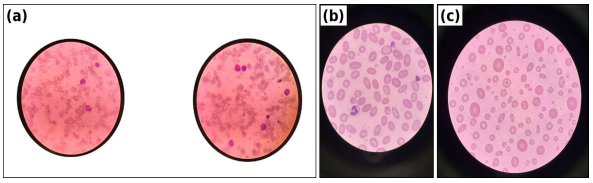

Fig. 1 Peripheral blood smear photomicrographs showing megaloblastic features. *a* Smear from patient A showing macrocytic dimorphic anaemia with nucleated red blood cells. *b* Smear from patient J showing numerous macro-ovalocytes with hypersegmented neutrophils. *c* Smear from patient D showing a dimorphic red-cell population with marked anisopoikilocytosis, consistent with coexisting iron deficiency

3.4 Dermatological findings

Cutaneous hyperpigmentation, a recognised but underappreciated mucocutaneous manifestation of cobalamin deficiency, was documented photographically in this series. Symmetrical hyperpigmentation over the knuckles and proximal interphalangeal joints was evident in patient A (Fig. 2a), patient C (Fig. 2b), and patient D (Fig. 2c), with a similar pattern observed in another patient from the series (Fig. 2d). Patient J additionally demonstrated hyperpigmentation of the malar and perioral facial skin (Fig. 2e). These pigmentary changes were not associated with any other mucocutaneous abnormality such as vitiligo or hair depigmentation, and were not accompanied by clinical or biochemical features suggestive of Addison disease.

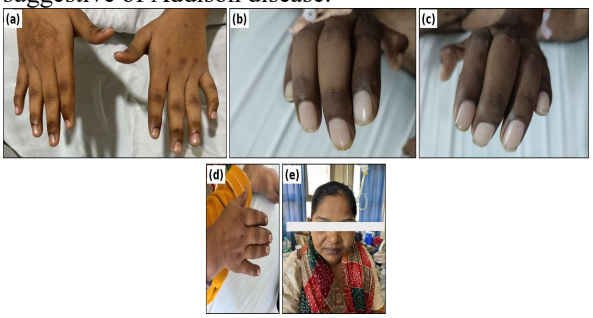

Fig. 2 Cutaneous hyperpigmentation observed in patients with vitamin B12 deficiency. *a* Hyperpigmented knuckles in patient A. *b* Hyperpigmented knuckles in patient C. *c* Knuckle hyperpigmentation in patient D. *d* Knuckle hyperpigmentation in another patient from the series. *e* Facial (malar and perioral) hyperpigmentation in patient J. Eyes have been masked to preserve patient anonymity; photographs are reproduced with written informed consent

3.5 Illustrative case vignettes

To illustrate the clinical spectrum encountered in this series, three representative cases are described in detail below.

Case A.

A 19-year-old man presented with several weeks of progressive fatigue and generalised weakness. Examination revealed pallor and hyperpigmented knuckles (Fig. 2a). Investigations showed haemoglobin 5.8 g/dL, total leukocyte count 3,050/cumm, platelet count 60,000/mm3, and MCV 134 fL—the most severe haematological derangement in the series. Peripheral smear showed macrocytic dimorphic anaemia with nucleated red blood cells (Fig. 1a). Serum vitamin B12 was 159 pg/mL. He showed marked symptomatic and haematological improvement following parenteral B12 replacement.

Case D.

A 29-year-old woman presented with fatigue and weakness. She had haemoglobin 10.6 g/dL (the highest in the series), total leukocyte count 4,100/cumm, platelet count 99,000/mm3, and MCV 118 fL, with serum B12 of 200 pg/mL—the least severe biochemical deficiency in the cohort, illustrating that even relatively modest reductions in serum cobalamin can be associated with pancytopenia. Peripheral smear revealed a dimorphic red-cell population with marked anisopoikilocytosis (Fig. 1c), and she had visible knuckle hyperpigmentation (Fig. 2c).

Case J.

A 31-year-old woman presented with fatigue and weakness and was noted to have both knuckle and facial hyperpigmentation (Fig. 2e), the most extensive cutaneous involvement in the series. Haemoglobin was 8.3 g/dL, total leukocyte count 3,600/cumm, and platelet count 76,000/mm3, with MCV 127 fL and serum B12 of 181 pg/mL. Peripheral smear showed numerous macro-ovalocytes with hypersegmented neutrophils (Fig. 1b), the classical morphological hallmark of megaloblastic anaemia.

3.6 Treatment and outcomes

All 11 patients were admitted for further evaluation and management and received parenteral vitamin B12 supplementation after other haematological, infectious, and malignant causes of pancytopenia had been excluded. Supportive measures, including nutritional counselling and correction of any associated micronutrient deficiency, were provided as indicated, and patients were monitored clinically and with serial haematological investigations during admission.

Nine of the 11 patients (82%) reported significant symptomatic improvement—including reduced fatigue, generalised weakness, and exertional intolerance—before discharge. Repeat serum vitamin B12 levels obtained prior to discharge had risen markedly, to between 900 and 1000 pg/mL in most patients, confirming adequate replenishment of body stores. Serial complete blood counts demonstrated early haematological recovery, with stabilisation of

haemoglobin, improving leukocyte and platelet counts, and biochemical evidence of reticulocytosis, indicating restoration of effective marrow erythropoiesis. No adverse effects attributable to parenteral B12 therapy were observed during hospitalisation.

Eight of the 11 patients (73%) attended outpatient follow-up four weeks after discharge. These patients showed continued clinical improvement together with further recovery of haemoglobin, leukocyte, and platelet counts, which approached normal reference ranges, alongside a persistently elevated reticulocyte count reflecting an appropriate marrow response. None of the patients who completed follow-up required re-hospitalisation or additional haematological intervention.

4. Discussion

Vitamin B12 deficiency is among the most common, and most readily treatable, causes of pancytopenia encountered in general medical practice, yet it continues to be under recognised—particularly when its presentation departs from the textbook picture of isolated macrocytic anaemia [1,5–9]. In the present series, all 11 patients presented with the non-specific complaints of fatigue and generalised weakness, and the diagnosis of pancytopenia—and subsequently of severe cobalamin deficiency—was made only after admission and structured haematological evaluation. This observation underscores that severe, multilineage haematological compromise can develop insidiously and remain clinically silent until advanced, reinforcing the value of a low threshold for obtaining a complete blood count, and subsequently a vitamin B12 assay, in patients with otherwise unexplained constitutional symptoms.

Multiple hospital-based series from across India have identified megaloblastic anaemia, almost always attributable to cobalamin (with or without folate) deficiency, as the leading or among the leading causes of pancytopenia, frequently rivalling aplastic anaemia, hypersplenism, and haematological malignancy [5–9]. Premkumar et al., in a study of 140 patients with pancytopenia from north India, found megaloblastic anaemia in 60.7% of cases, with severe cobalamin deficiency (B12 <100 pg/mL) present in 81% of all pancytopenic patients and in 91.6% of those with confirmed megaloblastic anaemia [6]. This high background prevalence is attributable to the predominantly vegetarian dietary pattern of large segments of the Indian population, compounded by socioeconomic constraints on dietary diversity and a substantial burden of chronic gastrointestinal disorders that impair cobalamin absorption [10–14]; population-based estimates of cobalamin deficiency or insufficiency among Indian vegetarians range from approximately 50% to over 70% [11,14].

The mechanism by which cobalamin deficiency produces pancytopenia, rather than isolated anaemia, relates to its essential role in DNA synthesis across all proliferating haematopoietic cell lines. Impaired thymidylate synthesis leads to asynchronous nuclear–cytoplasmic maturation ("megaloblastic" change) not only in erythroid precursors but also in granulocytic and megakaryocytic lineages, resulting in ineffective haematopoiesis and intramedullary destruction of abnormal precursors; this can produce a markedly hypercellular marrow despite peripheral cytopenia, and, in severe cases, biochemical and morphological findings—schistocytosis, low haptoglobin, markedly elevated lactate dehydrogenase, and thrombocytopenia—that closely mimic thrombotic thrombocytopenic purpura, a phenomenon termed pseudo-thrombotic microangiopathy [18–21]. Although none of our patients had the florid haemolytic picture characteristic of pseudo-thrombotic microangiopathy, awareness of this mimicry is clinically important, since failure to consider vitamin B12 deficiency in the differential diagnosis of apparent microangiopathic haemolytic anaemia can lead to unnecessary and potentially harmful plasma exchange [18–21].

A particularly important observation in our series, and one with direct diagnostic implications, is the presence of features suggesting concurrent iron deficiency in some patients, manifest as a dimorphic red-cell population on peripheral smear rather than pure macrocytosis (Fig. 1c). Combined iron and cobalamin deficiency is well described and is particularly common in populations, such as ours, with limited dietary diversity and a high prevalence of both nutrient deficiencies [15–17]. Because iron deficiency produces microcytic red cells while cobalamin deficiency produces macrocytic red cells, the two populations can numerically average out, yielding a deceptively normal—or even low—MCV despite ongoing megaloblastic erythropoiesis [15–17]. This "masking" phenomenon is a well-recognised diagnostic trap: clinicians who rely solely on the MCV or on the overall peripheral smear impression may diagnose and treat only the iron-deficiency component, leaving the cobalamin deficiency to progress unchecked until it manifests as pancytopenia, as appears to have occurred in several of our patients. This reinforces the recommendation that serum vitamin B12 be assessed liberally in anaemic patients—even those with a normal or low MCV—particularly when the degree of anaemia, the presence of additional cytopenias, or the clinical picture (disproportionate constitutional symptoms, neurological complaints, or cutaneous hyperpigmentation) is out of proportion to what iron

deficiency alone would be expected to produce [15–17].

Cutaneous hyperpigmentation, observed in four of our 11 patients, is a recognised but underappreciated mucocutaneous manifestation of cobalamin deficiency, reported in approximately one in five affected patients in published series, typically over the knuckles, dorsa of the hands and feet, and flexural and oral mucosal surfaces, and occasionally—as in our patient J—involving the face [22–24]. The proposed mechanism involves cobalamin-dependent dysregulation of melanocyte redox homeostasis, with increased reactive oxygen species generation, depletion of reduced glutathione, and consequent upregulation of tyrosinase activity and melanin synthesis [23,24]. This pigmentary change is typically reversible with cobalamin replacement and, when recognised, can serve as a valuable bedside clue prompting earlier vitamin B12 testing, particularly in patients with pigmented skin in whom subtle pallor may otherwise be more difficult to appreciate clinically [22–24].

All patients in our series were treated with parenteral cobalamin replacement, in keeping with standard practice for patients with severe deficiency, neurological involvement, or suspected malabsorption, in whom parenteral therapy achieves more rapid and reliable repletion than the oral route [1,17]. The clinical and haematological response observed in our cohort—symptomatic improvement in the majority of patients prior to discharge, a rise in serum B12 to replacement-phase levels, and progressive normalisation of haemoglobin, leukocyte, and platelet counts with reticulocytosis on follow-up—is entirely consistent with the expected natural history of treated cobalamin-deficiency pancytopenia, which typically shows reticulocytosis within 3–5 days and substantial haematological recovery within 4–8 weeks of adequate replacement [1,17]. Importantly, no adverse effects of therapy were observed, reaffirming the safety of parenteral vitamin B12 supplementation even in patients with profound cytopenia.

From a health-systems perspective, the findings of this series have practical implications. Because megaloblastic anaemia secondary to cobalamin deficiency is inexpensive to diagnose (a single serum B12 assay) and treat (low-cost parenteral cobalamin), early recognition can spare patients from unnecessary, costly, and invasive investigations—including bone marrow aspiration/biopsy, extensive infectious and autoimmune work-up, or, in the setting of pseudo-thrombotic microangiopathy, urgent plasma exchange—that are otherwise indicated in the broader differential diagnosis of pancytopenia [4,6,18–21]. A pragmatic diagnostic approach in resource-limited settings, supported by several Indian series, is to screen all patients with unexplained pancytopenia for serum vitamin B12 (and folate) at the outset, reserving bone marrow examination for patients without an identifiable nutritional cause or those who fail to respond appropriately to replacement therapy [6,9].

4.1 Limitations

This series has the inherent limitations of a small, single-centre, retrospective case series without a comparator group. Methylmalonic acid and homocysteine assays, which offer greater sensitivity for confirming functional cobalamin deficiency, anti-intrinsic factor and anti-parietal cell antibody testing to specifically identify pernicious anaemia, and bone marrow examination were not performed in all patients, as the combination of pancytopenia, megaloblastic peripheral smear morphology, and a markedly reduced serum B12 level was considered sufficient for diagnosis once other causes had been reasonably excluded; this approach is consistent with that adopted in several other Indian series [6,9]. Follow-up was available in only 8 of 11 patients and was limited to four weeks, precluding assessment of long-term haematological and neurological outcomes or relapse. Finally, as a descriptive case series, no causal inferences beyond the temporal association between cobalamin replacement and clinical/haematological recovery can be drawn.

5. Conclusion

Vitamin B12 deficiency remains an important, common, and entirely reversible cause of pancytopenia, particularly in populations with a predominantly vegetarian diet and limited dietary diversity. The present series of 11 patients illustrates the diagnostic value of an elevated MCV and characteristic peripheral smear findings, while also highlighting the diagnostic pitfall posed by coexisting iron deficiency, which can mask the classical macrocytic picture and delay recognition. Cutaneous hyperpigmentation, when present, offers a useful additional clinical clue. A high index of suspicion, supported by timely serum vitamin B12 assay, allows early diagnosis and prompt, low-cost, and effective treatment with parenteral cobalamin, thereby avoiding unnecessary invasive investigations and preventing progression to more severe haematological or neurological complications.

Declarations

Consent for publication

Written informed consent was obtained from all patients for publication of their de-identified clinical images and data in this article. Identifying features have been masked wherever necessary to protect patient anonymity.

Availability of data and materials

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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