

LETTER TO THE EDITOR

Transfusion-refractory pancytopenia with MDS-like morphologic alterations of the bone marrow in a 29-year old man: A mimicry manifestation caused by scurvy

Scurvy is ancient disease caused by low or depleted levels of vitamin C (ascorbic acid, VITC) and described throughout history. It is recognized as “sailors' deadly disease” and nowadays found in developing countries or under desolate social conditions.¹ Symptoms comprise myalgia, arthralgia, periodontal bleeding, bleedings of extremities, and anaemia. Low VITC levels in serum or leukocytes are used for diagnosis. With VITC supplementation, the prognosis is excellent and symptoms resolve within a short time, whereas scurvy is usually fatal if untreated.²

Literature describes cases of pancytopenia and bone marrow abnormalities in scurvy.^{3–6} MDS (myelodysplastic

syndrome)-like bone marrow manifestations haven't been reported, yet.

A 29-year-old man in reduced general condition (BMI: 18.2 kg/m²) presented to hospital. He suffered from anaemia (haemoglobin: 74 g/l, leucocytes: 3.71/nl, platelets: 146/nl), elevated inflammation parameters (C-reactive protein: 7.5 mg/dl), and edematous swelling of the thighs. Initial symptom onset was 3 years ago, following ciprofloxacin-based treatment of prostatitis. Clinical examination revealed non-palpable purpura of extremities (Figure 1A). Deep vein thrombosis and infections were excluded. Sonography and MRI of thighs and pelvis showed diffuse edemas and

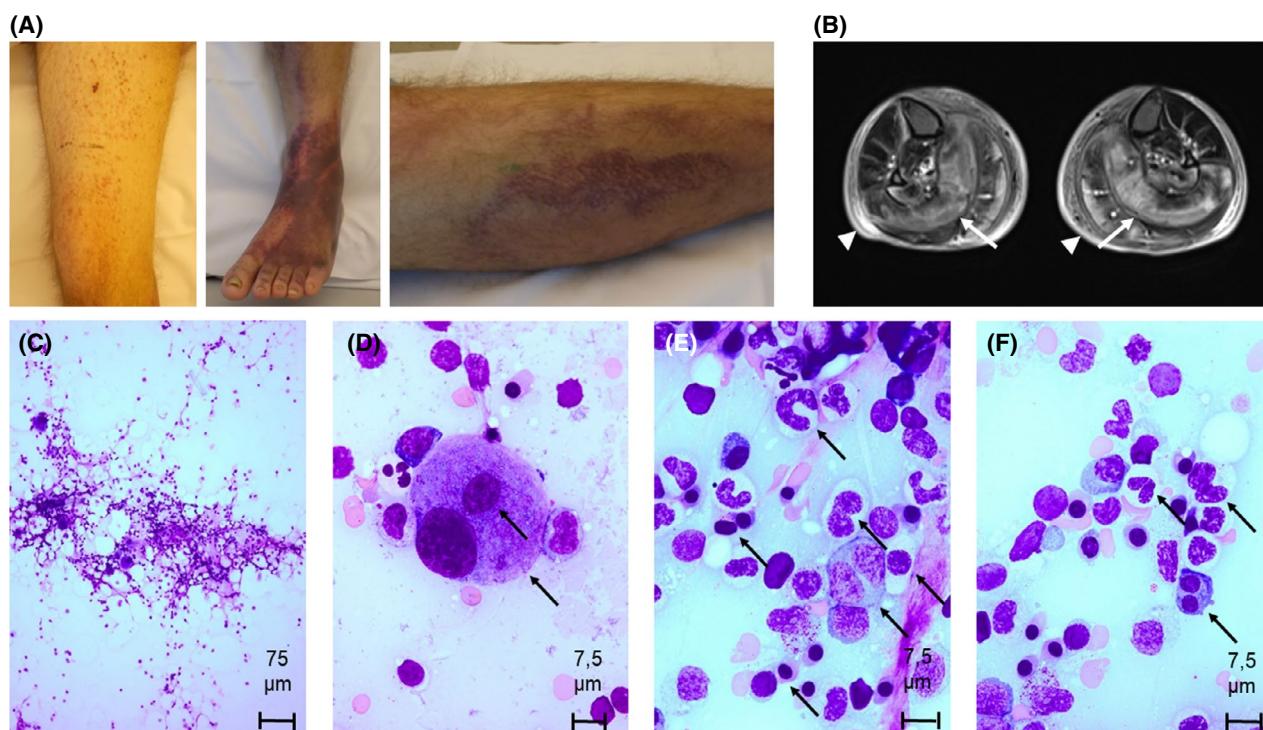


FIGURE 1 Clinical presentation of scurvy, magnetic resonance tomography (MRI) imaging of thighs, cytology of bone marrow aspiration in scurvy (A) purpura/panniculitis of the right thigh (left) and diffuse ecchymosis of the left forefoot (middle) and lower leg (right); (B) MRI-imaging of the lower legs with diffuse subcutaneous edema (white arrow-heads) and MRI-signs interpreted as potential myositis (white arrows); (C) hypoplastic cytology in bone marrow aspirate (magnification: 100×, Papanicolaou-staining); (D–F) dysplasia of haematopoiesis as described in the manuscript (black arrows) (all magnification 1000×, all Papanicolaou-staining)

unspecific signs of myositis (Figure 1B). Anaemia diagnostics revealed iron deficiency (transferrin: 201 mg/dl, transferrin saturation: 7.4%, ferritin: 193 ng/ml), borderline normal cyanocobalamin (290 pg/ml) and low folate levels (3.8 ng/ml). Vitamin B1, B6, and D were normal. The reticulocyte reproduction index was decreased (0.6). No hemolysis (haptoglobin: 217 mg/dl, lactate dehydrogenase: 210 U/l, no schistocytes), infections (hepatitis B/C, HIV, CMV, EBV, Hantavirus) or signs of rheumatologic disease were detected. Steroid, iron, and vitamin applications (folate, cyanocobalamin) did not lead to haematological improvement. The patient refused endoscopy for exclusion of gastrointestinal bleeding.

Due to transfusion refractory anaemia, worsening pancytopenia (haemoglobin: 50 g/l, leucocytes: 1.88/nl, platelets: 88/nl), and ecchymosis (Figure 1A), the patient was relocated to the Department of Haematology. To further investigate deteriorating pancytopenia, bone marrow biopsy was assessed. Viral infections (HSV, CMV, EBV, VZV, HHV6, Parvovirus B19) were excluded. Cytology showed hypocellularity with non-significant dysplasia of all three lineages (Figure 1C). Particularly, pyknotic and oval nuclei of erythroid precursors, megakaryocytes with bizarre nucleus configuration, erythroid cells with double nuclei, giant rod-cored and pseudo Pelger-Huët cells, and a general shift

of nucleus-plasma relation were detectable (Figure 1D–F). Histology showed elevated iron reservoirs and immature megakaryopoiesis. Immunophenotyping and NGS-based genetic diagnostics (AmpliSeq for Illumina Myeloid Panel) did not indicate hematologic neoplasms or clonal aberrations. In summary, MDS-like morphological alterations without evidence of clonality were observed.

Upon repeated detailed inquiry, the patient reported extensive weight loss (a pp. 35 kg within 8 months) and diet with exclusion of fruits and vegetables because of self-suspected sprue and lactose/fructose intolerance. Psychiatric counselling excluded eating disorders.

Based on this information VITC levels were assessed and showed absolute deficiency (serum level: <0.5 mg/dl, reference: 2–20 mg/dl). Upon daily administration of 1 g VITC, pancytopenia improved (Figure 2A), purpura and ecchymosis decreased and the patient was finally discharged. Unfortunately, the patient was lost to follow-up including further clinical or laboratory controls.

VITC is an essential, water-soluble vitamin and mainly found in fruits and vegetables. Most animals except humans can synthesize VITC.² Minimum serum levels are unknown, however, patients become symptomatic at concentrations of 1.4 mg/dl and below. As VITC is essential for enzymatic processes in the nervous system, fatty acid metabolism, and

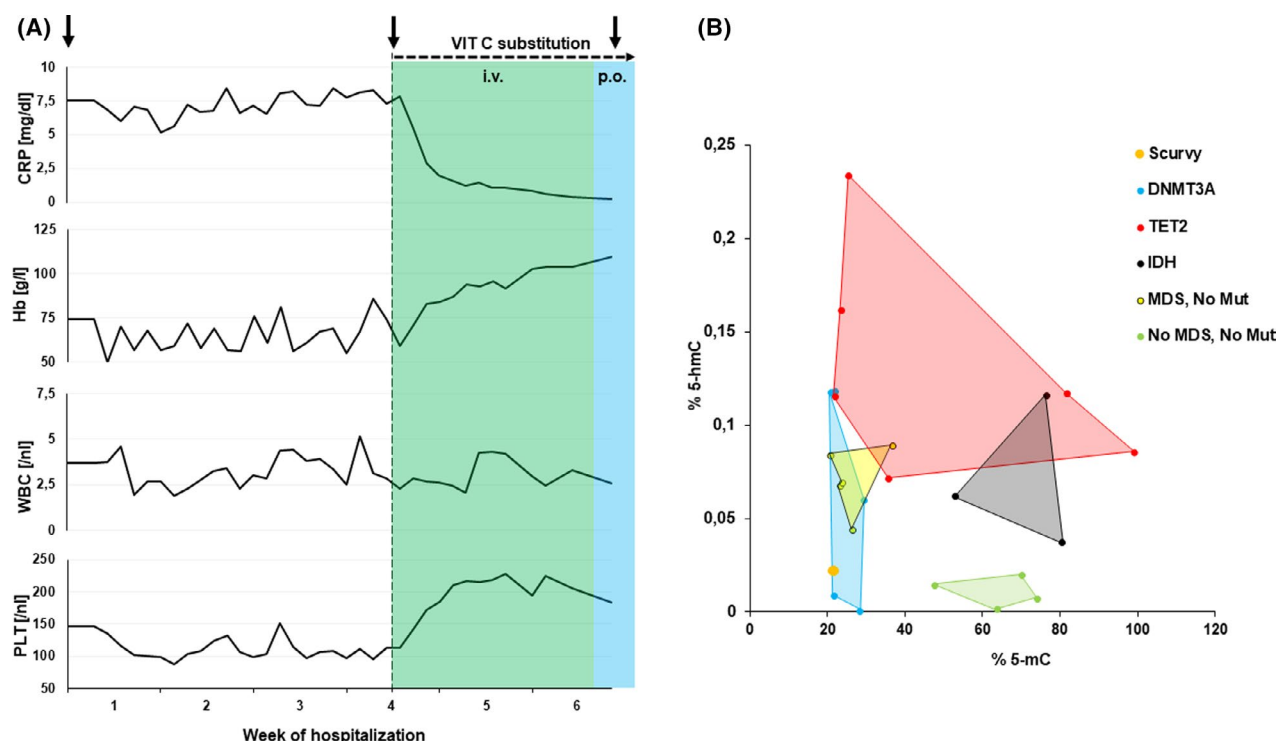


FIGURE 2 Course of laboratory parameters over hospitalization (A). Diagram of concentrations of 5-hmC (5-hydroxymethylcytosine) and 5-mC (5-methylcytosine) in bone marrow mononuclear cells of scurvy and MDS patients and healthy donors (B). (A) levels of haemoglobin (Hb), white blood cells (WBC), platelets (PLT), and elevated levels of C-reactive protein (CRP) over time of hospitalization, onset and time (dashed arrow) of vitamin C (VITC) substitution (intravenous (i.v.), green area; per os (p.o.): blue area) beyond hospitalized stay, black arrows: hospital admission, onset of VITC substitution, release from hospital; (B) “clustering” of bone marrow mononuclear cells according to their global content of 5-hmC (y-axis) and 5-mC (x-axis) grouped by their mutational status. Each dot represents the mean values of a patient sample measured in triplicates; *DNMT3A*, DNA methyltransferase 3 alpha; *IDH1/2*, Isocitrate dehydrogenase 1/2; Mut, Mutation; *TET2*, Ten eleven transferase 2; wtMDS: Wildtype MDS

collagen synthesis, deficiency causes psychiatric symptoms and connective tissue malfunction like bleeding.

Impact of VITC on haematopoiesis depends on its role in iron metabolism, where it is relevant for enteral absorption and oxidation control.⁷ Increased response to erythropoietin is observed, when VITC is substituted in addition to iron,^{8–10} however, mechanisms of VITC associated haematopoietic defects are incompletely understood. The impact of VITC as a cofactor for epigenetic gene regulation has been described for the function of methylcytosine dioxygenase TET2 mediated demethylation of CpG dinucleotides in regulatory DNA regions. In MDS, distinct genetic alterations in the epigenetic modifier genes *TET2*, *IDH1/2*, and *DNMT3A* alter haematopoietic differentiation by disturbed DNA de-/methylation processes leading to bone marrow dysplasia.¹¹ Specifically, TET2 malfunction, e.g. by mutation, has been implicated with pathogenesis of AML and MDS.^{12,13} Consequently, hypovitaminosis C may mimic TET2 loss-of-function and lead to insufficient conversion to hydroxymethylation.^{10–12}

We assessed global levels 5-methyl-cytosine (5-mC) and 5-hydroxymethyl-cytosine (5-hmC) by ELISA (Zymo Research Quest 5-hmC DNA ELISA and 5-mC DNA ELISA) as surrogate parameters for TET2-dependent DNA demethylation.^{11,12} 24 cases (including one case of scurvy, 19 cases of MDS [five *DNMT3A*-mutated, six *TET2*-mutated, three *IDH1/2*-mutated, 5 *DNMT3A*-, *TET2*-, and *IDH1/2*-wildtype], four bone marrow samples from healthy donors) were analysed. Overall, 5-hmC levels in scurvy were diminished beyond levels in MDS. 5-mC levels of scurvy were comparable to *DNMT3A* mutated or wildtype MDS cases, while *TET2*- and *IDH1/2*-mutated MDS showed increased DNA methylation levels (Figure 2B). Cases without MDS showed low 5-hmC levels and high 5-mC levels. These data suggest that impaired regulation of DNA (hydroxy)-methylation might be linked to scurvy-associated disturbances in myeloid differentiation mimicking MDS-like morphology. While MDS is a disease characterized by clonal aberrations, “dysplasia” in scurvy is not determined genetically. Our observations suggest altered DNA methylation and minimum 5-hmC levels by diminished TET2-dependent DNA demethylation in absence of VITC in scurvy to cause a MDS-like phenotype.

This case highlights transfusion-refractory pancytopenia with morphology of a MDS-like mimicry in the bone marrow as one manifestation of scurvy. Furthermore, it suggests functional analogy between scurvy and MDS through altered epigenetic regulation as a cause of mimicry of MDS-related changes. More profound epigenomic diagnostics are needed.

Scurvy is rare and VITC deficiency may be missed in clinical routine. It needs to be considered in cases of malnutrition, in patients with hematologic diseases, and in patients undergoing therapy. A recent study reported increased inflammation in neutropenic patients with low levels of VITC undergoing myeloablative chemotherapy.¹⁴ Thus, relevant complications such as inadequate haematopoiesis with prolonged aplasia, elevated inflammatory parameters, and

extensive antibiotic administration must be considered and are of clinical relevance.

CONFLICT OF INTEREST

All authors declare no competing interests.

AUTHOR CONTRIBUTIONS

PM, RC: Study design, data acquisition, data interpretation, clinical treatment of patient, manuscript drafting. TG: Study design, data acquisition, data interpretation, manuscript drafting. CS, MT, TP: Clinical treatment of patient, manuscript drafting. GF, AR, KH: Routine diagnostics, clinical treatment of patient, review of manuscript. BM, MH: Routine diagnostics, review of manuscript.

FUNDING INFORMATION

No third party funding.

Patrick Mayr¹ 
 Tatiana Grünewald¹
 Giuliano Filippini Velazquez¹
 Andreas Rank¹
 Christoph Schmid¹
 Manuela Harloff²
 Bruno Märkl²
 Martin Trepel¹
 Klaus Hirschbühl¹
 Tim Pfeiffer¹
 Rainer Claus^{1,2}

¹Hematology and Oncology, Medical Faculty,
 University of Augsburg, Augsburg, Germany
 Email: patrick.mayr@uk-augsburg.de

²General Pathology and Molecular Diagnostics,
 Medical Faculty, University of Augsburg, Augsburg,
 Germany
 Email: rainer.claus@uk-augsburg.de

ORCID

Patrick Mayr  <https://orcid.org/0000-0002-3416-3225>

REFERENCES

1. Clemeston CAB. Vitamin C. Boca Raton: CRC Press; 1989. p. 336.
2. Padayatty SJ, Levine M. Vitamin C: the known and the unknown and goldilocks. *Oral Dis.* 2016;22(6):463–93.
3. Lal A, Mishra AK, Sahu KK, Noreldin M. Scurvy of modern age: rare presentation with pancytopenia. *Blood Cells Mol Dis.* 2019;77:76–7.
4. Benezech S, Hartmann C, Morfin D, Bertrand Y, Domenech C. Is it leukemia, doctor? No, it's scurvy induced by an ARFID! *Eur J Clin Nutr.* 2020;74(8):1247–9.
5. Yang G, Hanna CM. Hematopoietic findings in a patient with scurvy. *Blood.* 2019;134(25):2330.
6. Alhatem A, Cai D. Behind the skin: A rare case of scurvy-associated megaloblastic anemia. *Clin Med Insights: Case Rep.* 2019;12:1–4.
7. Lane DJ, Richardson DR. The active role of vitamin C in mammalian iron metabolism: much more than just enhanced iron absorption! *Free Radic Biol Med.* 2014;75:69–83.
8. Sultana T, DeVita MV, Michelis MF. Oral vitamin C supplementation reduces erythropoietin requirement in hemodialysis patients with functional iron deficiency. *Int Urol Nephrol.* 2016;48(9):1519–24.

9. Deicher R, Ziai F, Habicht A, Bieglmayer C, Schillinger M, Horl WH. Vitamin C plasma level and response to erythropoietin in patients on maintenance haemodialysis. *Nephrol Dial Transplant*. 2004;19(9):2319–24.
10. Gonzalez-Menendez P, Romano M, Yan H, Deshmukh R, Papoin J, Oburoglu L, et al. An IDH1-vitamin C crosstalk drives human erythroid development by inhibiting pro-oxidant mitochondrial metabolism. *Cell Rep*. 2021;34(5):108723.
11. Pasca S, Jurj A, Zdrengea M, Tomuleasa C. The potential equivalents of TET2 mutations. *Cancers*. 2021;13(7):1499.
12. Solary E, Bernard OA, Tefferi A, Fuks F, Vainchenker W. The ten-eleven Translocation-2 (TET2) gene in hematopoiesis and hematopoietic diseases. *Leukemia*. 2014;28(3):485–96.
13. Cimmino L, Dolgalev I, Wang Y, Yoshimi A, Martin GH, Wang J, et al. Restoration of TET2 function blocks aberrant self-renewal and leukemia progression. *Cell*. 2017;170(6):1079, e20–95.
14. Carr AC, Spencer E, Das A, Meijer N, Lauren C, MacPherson S, et al. Patients undergoing myeloablative chemotherapy and hematopoietic stem cell transplantation exhibit depleted vitamin C status in association with febrile neutropenia. *Nutrients*. 2020;12(6):1879.