BLEEDING NEUROFIBROMA AS A MANIFESTATION OF NF1-ASSOCIATED VASCULOPATHY WITH CONCOMITANT GASTROINTESTINAL STROMAL TUMOR : A RARE CASE REPORT

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ABSTRAK

Neurofibromatosis tipe 1 (NF1) merupakan kelainan genetik autosomal dominan yang ditandai oleh manifestasi multisistem, termasuk predisposisi terhadap tumor dan kelainan vaskular. Salah satu komplikasi yang jarang dilaporkan adalah perdarahan aktif dari neurofibroma kutan akibat vasculopathy yang terkait dengan NF1. Gastrointestinal stromal tumor (GIST) juga memiliki hubungan erat dengan NF1, terutama muncul di usus halus, bersifat multifokal, dan sering kali tidak menunjukkan mutasi KIT maupun PDGFRA. Laporan kasus ini mendeskripsikan seorang perempuan berusia 53 tahun dengan riwayat NF1 yang datang ke unit gawat darurat dengan anemia akut akibat perdarahan aktif dari neurofibroma ulseratif di regio gluteal, serta riwayat GIST berisiko tinggi yang sebelumnya telah direseksi. Pemeriksaan fisik menunjukkan tanda khas NF1 berupa café-au-lait macules, neurofibroma multipel, dan nodul Lisch. Pemeriksaan laboratorium mengungkapkan hemoglobin 5,2 g/dL dengan leukositosis, sedangkan pencitraan abdomen menunjukkan massa mesenterik besar yang sesuai dengan GIST. Penatalaksanaan meliputi transfusi darah, perawatan luka lokal, serta terapi suportif, dengan perbaikan klinis meskipun pasien menolak tindakan eksisi lebih lanjut. Kasus ini menyoroti peran vasculopathy NF1 dalam meningkatkan fragilitas vaskular neurofibroma sehingga memicu perdarahan signifikan, serta kompleksitas prognosis pada pasien dengan kombinasi NF1 dan GIST.

Kata kunci : neurofibroma kutaneus, neurofibromatosis tipe 1, NF1, Tumor Stroma Gastrointestinal (GIST), vaskulopati terkait NF1

ABSTRACT

Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder characterized by multisystem involvement, including tumor predisposition and vascular abnormalities. One of the rare complications reported is active bleeding from cutaneous neurofibromas due to NF1-associated vasculopathy. Gastrointestinal stromal tumors (GISTs) also show a strong association with NF1, typically arising in the small intestine, often multifocal, and frequently lacking KIT or PDGFRA mutations. This case report describes a 53-year-old female with NF1 who presented to the emergency department with acute anemia caused by active bleeding from an ulcerated neurofibroma in the gluteal region, along with a history of a previously resected high-risk GIST. Physical examination revealed classical NF1 features, including café-au-lait macules, multiple cutaneous neurofibromas, and Lisch nodules. Laboratory findings showed severe anemia (hemoglobin 5.2 g/dL) with leukocytosis, while abdominal imaging demonstrated a large mesenteric mass consistent with GIST. Management included blood transfusion, local wound care, and supportive therapy, resulting in clinical improvement despite the patient's refusal of surgical excision. This case highlights the role of NF1-associated vasculopathy in increasing vascular fragility within neurofibromas, leading to significant hemorrhage, as well as the complex prognosis in patients with concurrent NF1 and GIST.

Keywords *: neurofibromatosis type 1, NF1, cutaneous neurofibroma, NF1-associated vasculopathy, Gastrointestinal Stromal Tumor, GISTs*

INTRODUCTION

Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder caused by pathogenic variants in the *NF1* gene, resulting in dysregulation of the RAS/MAPK signaling pathway and a predisposition to tumor development (Riccardi, 1992). NF1 is characterized by café-au-lait macules, axillary or inguinal freckling, Lisch nodules, and multiple cutaneous neurofibromas (Riccardi, 1992; Friedman, 2020). NF1 is a multisystem disease associated with an increased risk of various benign and malignant neoplasms, as well as vascular abnormalities (Friedman, 2020). Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract and show a well-established association with NF1 (Miettinen, 2006). NF1-associated GISTs typically arise in the small intestine, are frequently multifocal, and often lack activating *KIT* or *PDGFRA* mutations, distinguishing them from sporadic GISTs (Miettinen, 2006; Agaimy, 2012). Recent systematic reviews have demonstrated a significant prevalence of small intestinal GISTs among patients with NF1 (Yamamoto, 2009).

Neurofibromatosis type 1 (NF1) has an estimated global prevalence of approximately 1 in 2,500–3,000 individuals, with comparable figures reported across Asian populations. NF1 is associated with increased morbidity and reduced survival, with a reported reduction in life expectancy of 8–15 years, primarily due to malignant and vascular complications. Gastrointestinal stromal tumors (GISTs) occur in approximately 5–25% of NF1 patients and account for 3–6% of all GIST cases in Asian cohorts, typically arising in the small intestine and often presenting as multifocal lesions. Although NF1-associated GISTs generally demonstrate a more indolent biological behavior than sporadic GISTs, patients with high-risk tumor features or concurrent NF1-associated vasculopathy may experience poorer outcomes, underscoring the need for long-term surveillance and comprehensive risk assessment. In addition to tumor predisposition, NF1 is increasingly recognized as a disorder associated with vasculopathy. NF1-associated vasculopathy encompasses a spectrum of vascular abnormalities, including arterial stenosis, aneurysm formation, arteriovenous malformations, and vascular fragility, which may occur due to dysplasia of the vessel wall and abnormal proliferation of vascular smooth muscle cells (Uusitalo, 2015; Oderich, 2007).

These vascular changes may predispose patients to spontaneous bleeding and hemorrhagic complications, even in the absence of overt trauma. Although anemia in patients with GIST is commonly attributed to gastrointestinal bleeding, active bleeding from cutaneous neurofibromas is rare (Fetsch, 1997). Ulceration and hemorrhage of neurofibromas are uncommon but potentially life-threatening complications and may be related to underlying NF1-associated vasculopathy and vascular fragility within the tumor. We report a rare case of acute anemia caused by active bleeding from an ulcerated cutaneous neurofibroma in a patient with NF1 and a history of a previously resected high-risk GIST, highlighting the complex interplay between NF1-associated vasculopathy, tumor biology, and prognostic risk factors.

METHOD

This study employed a case report design aimed at comprehensively describing the clinical manifestation of bleeding neurofibroma as part of neurofibromatosis type 1 (NF1)–associated vasculopathy with concomitant gastrointestinal stromal tumor (GIST). The subject of the study was a 53-year-old female diagnosed with NF1 who presented to the emergency department with active bleeding from an ulcerated neurofibroma lesion. Data were collected through detailed history taking, comprehensive physical examination, dermatological and ophthalmological assessments, as well as supporting investigations including laboratory tests and radiological imaging. The diagnosis of NF1 was established based on accepted clinical

diagnostic criteria, while GIST was confirmed through intraoperative findings and histopathological examination. Additional clinical information was obtained from the patient's medical records, including previous medical history and response to treatment. Patient management consisted of supportive therapy, including blood transfusion and local wound care, followed by clinical evaluation. Data analysis was conducted descriptively with emphasis on the correlation between clinical manifestations, diagnostic findings, and the underlying pathophysiological mechanisms. The case report was prepared in accordance with the CARE (CAse REport) guidelines to ensure completeness and scientific rigor.

CASE REPORT

A 53-year-old female presented to the emergency department (ED) with a 3 day history of fever, generalized weakness, and active bleeding from an ulcerated lesion in the gluteal region. On admission, vital signs were as follows: temperature 37.8°C, heart rate 89 beats per minute, respiratory rate 18 breaths per minute, blood pressure 120/75 mmHg, and oxygen saturation 99% on room air. Physical examination revealed typical features of neurofibromatosis type 1 (NF1), including café-au-lait macules, multiple cutaneous neurofibromas, and Lisch nodules. Dermatological examination demonstrated numerous cutaneous neurofibromas predominantly involving the trunk and extremities. The lesions appeared as soft, skin-colored to brownish nodules, ranging in size from a few millimeters to several centimeters in diameter, with some showing a pedunculated morphology (Figure 1). Multiple café-au-lait macules measuring greater than 1.2 cm in diameter were observed (Figure 2), along with axillary and inguinal freckling (Figure 3). A large ulcerated cutaneous neurofibroma was identified in the gluteal region, measuring several centimeters in diameter, with exposed friable tissue and active bleeding, consistent with the source of acute blood loss (Figure 4). Ophthalmologic examination revealed the presence of multiple Lisch nodules on the iris, further supporting the diagnosis of NF1 (Figure 5). Examination of the mucous membranes revealed no abnormalities.

The patient had a documented history of chronic anemia prior to surgical management of a gastrointestinal tumor, suggesting a longstanding underlying condition that may have contributed to reduced hematologic reserve. Laboratory evaluation on admission revealed severe acute anemia, with a hemoglobin level of 5.2 g/dL, consistent with acute blood loss secondary to active bleeding from the ulcerated neurofibroma. The patient also exhibited leukocytosis (18,610/µL), suggesting an ongoing inflammatory response associated with active hemorrhage. Contrast-enhanced abdominal imaging revealed a large mesenteric mass measuring approximately 12.5 × 6.6 × 15.5 cm, causing compression of the descending colon and suspicious for a gastrointestinal stromal tumor (GIST). An additional soft-tissue mass in the right upper abdominal wall, consistent with a cutaneous neurofibroma, was also noted. Surgical exploration revealed a well-circumscribed tumor, and histopathological examination confirmed a high-risk gastrointestinal stromal tumor, characterized by spindle-shaped cells with high mitotic activity.

The patient received supportive treatment, including transfusion of three units of packed red cells (PRC). Local wound care with topical antibiotic, corticosteroid, and keratolytic therapy resulted in improvement of the ulcerated lesion. Although surgical excision of the bleeding neurofibroma was advised, the patient declined further intervention and was discharged with stable vital signs and clinical improvement.

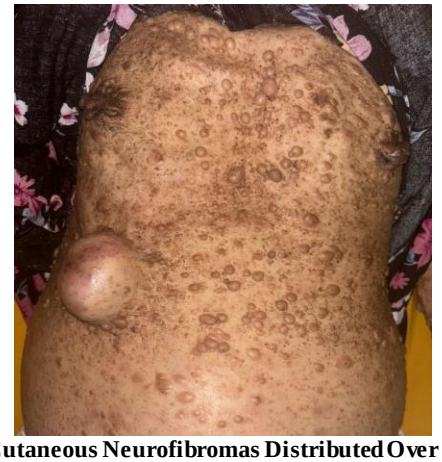

Figure 1. Multiplicity of Cutaneous Neurofibromas Distributed Over The Abdomen and Thorax

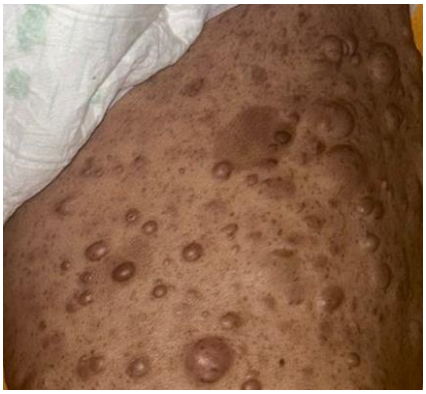

Figure 2. Café-Au-Lait Spot

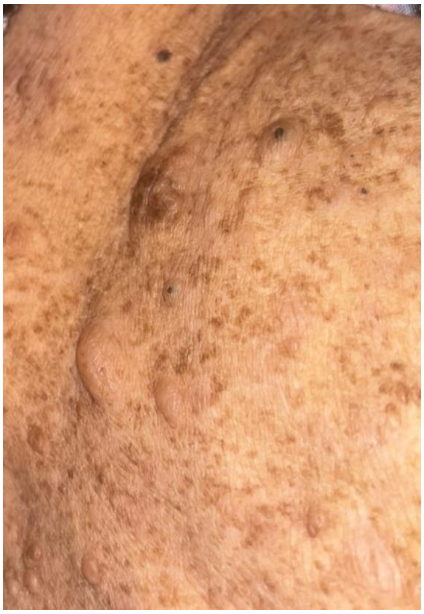

Figure 3. Axillary Freckling

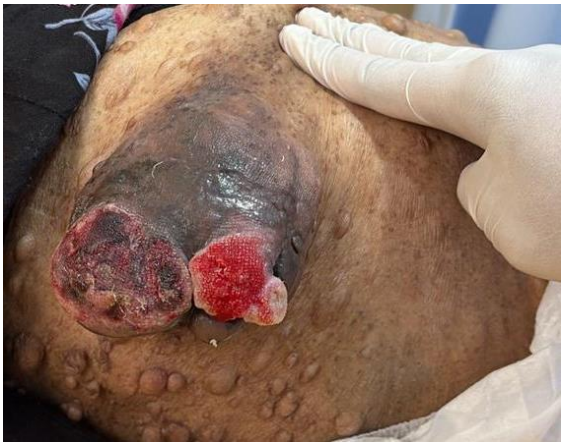

Figure 4. Actively Bleeding Ulcerated Cutaneous Neurofibroma In The Gluteal Region

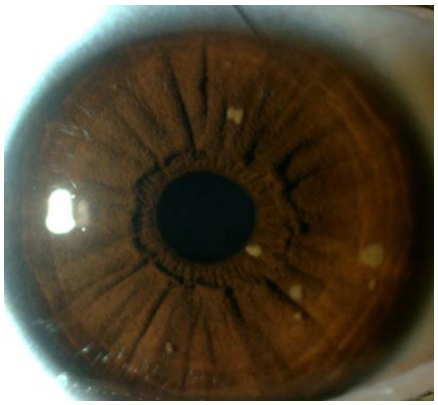

Figure 5. Lisch Nodules

DISCUSSION

Cutaneous neurofibromas are benign peripheral nerve sheath tumors composed of Schwann cells, fibroblasts, mast cells, and a fragile vascular network (Riccardi, 1992). Although most cutaneous neurofibromas are asymptomatic, they may occasionally undergo rapid growth, ulceration, or spontaneous bleeding due to vascular fragility, ischemic necrosis, or repeated mechanical trauma (Fetsch, 1997; Hirota, 20060. In patients with neurofibromatosis type 1 (NF1), these processes may be amplified by NF1-associated vasculopathy, which is characterized by dysplasia of the vessel wall, abnormal proliferation of vascular smooth muscle cells, and endothelial dysfunction secondary to dysregulation of the RAS/MAPK signaling pathway (Oderich, 2007; Friedman, 2002). In the present case, the patient developed severe acute anemia with a hemoglobin level of 5.2 g/dL, consistent with acute blood loss. The presence of leukocytosis supported an acute inflammatory response associated with active hemorrhage. The combination of NF1-associated vasculopathy, local ischemic ulceration, and fragile intratumoral vasculature likely played a central role in the development of persistent bleeding from the ulcerated neurofibroma.

The coexistence of NF1 and GIST is well documented. NF1-associated GISTs most commonly involve the jejunum or ileum and may present as large or multifocal tumors (Miettinen, 2006; Agaimy, 2012; Yamamoto, 2009). Compared with sporadic GISTs, NF1-associated tumors show distinct molecular characteristics and may demonstrate aggressive behavior depending on tumor size and mitotic activity (Agaimy, 2012; Yamamoto, 2009). In this patient, histopathological examination revealed a spindle-cell neoplasm with high mitotic activity, consistent with a high-risk GIST. While gastrointestinal bleeding from GISTs is a recognized cause of anemia, the absence of overt gastrointestinal hemorrhage and the presence

of an actively bleeding cutaneous lesion favored the ulcerated neurofibroma as the primary etiology. This case highlights the importance of recognizing NF1-associated vasculopathy as a contributing factor in ulcer formation and hemorrhagic complications of cutaneous neurofibromas.

CONCLUSION

Active bleeding from an ulcerated cutaneous neurofibroma is a rare but potentially life-threatening complication of neurofibromatosis type 1 that may result in severe acute anemia. NF1-associated vasculopathy and vascular fragility may contribute to ulceration and persistent hemorrhage. In patients with both cutaneous and visceral sources of bleeding should be systematically evaluated. Early recognition, multidisciplinary assessment, and prompt management are essential to reduce morbidity and improve clinical outcomes.

ACKNOWLEDGMENTS

The authors would like to express their sincere gratitude to all parties who contributed to the preparation and completion of this case report, particularly the Department of Dermatology and Venereology of Bhayangkara Hospital Level I, Pusdokkes Polri, East Jakarta, for the clinical and academic support provided. Appreciation is also extended to the medical and paramedical teams involved in the patient's care, as well as to the Faculty of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, for providing facilities and scientific guidance. The authors are also grateful to the patient and the patient's family for their cooperation, consent, and provision of necessary information, which enabled this case report to be properly prepared and published.

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