A case of jejunal neurofibroma in von Recklinghausen's disease with active hemorrhage, detected and located with gastrointestinal bleeding scintigraphy: A case report with literature review

Miloš Stević[1] MD, PhD,
Marina Vlajković[1] MD, PhD,
Filip Veličković[1] MD,
Goran Stanojević[2] MD, PhD,
Milica Nestorović[2] MD,
Filip Petrović[3] MD

1. Center for Nuclear Medicine, Clinical Center Nis, Serbia
2. Clinic of Gastrointestinal Surgery, Clinical Center Nis, Serbia
3. Center for Radiology, Clinical Center Nis, Serbia

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Corresponding author:
Milos Stevic MD, PhD
Clinical Center Nis, Center for Nuclear Medicine
Address: Bulevar Dr Zorana Djindjica 48, 18000 Nis, Serbia
mlsstvc@gmail.com
Phone: +381 69 309 30 39

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Abstract
A 69 year old patient was admitted to hospital with massive gastrointestinal hemorrhage. The clinical presentation of the patient, except for bleeding, was dominated by the presence of neurofibromatosis type 1 - Von Recklinghausen disease. The patient was referred to multislice computed tomography (CT) angiography, magnetic resonance imaging (MRI), esophagogastroduodenoscopy and colonoscopy, which were performed without successful detection of the bleeding site. The MRI examination showed the existence of a tumor located in the small pelvis. After that, gastrointestinal bleeding scintigraphy (GIBS) with technetium-99m (^{99m}Tc) pyrophosphate in vivo labeled erythrocytes was done. Gastrointestinal bleeding scintigraphy showed active intraluminal bleeding from the projection of jejunum, which flowed through the small intestine to the descending colon and the sigmoidal and rectal segment of the colon. Surgical resection of the abdomen revealed the existence of tumors in the jejunum with active bleeding and resection and anastomosis was done. Histopathological verification showed intestinal neurofibroma. In this case GIBS showed usefulness in proving the existence of active bleeding in the small intestine and its localization, and it was of a great help in planning the surgical treatment of a patient.

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Introduction

Neurofibromatosis type 1 or Von Recklinghausen's disease is a hereditary disease caused by a disorder on a gene located on the 17th chromosome that encodes the production of neurofibromin [1]. Neurofibromin is an essential negative regulator of Ras cellular proliferation pathways and because of that acts like suppressor compound for many types of tumors, and its impaired synthesis results in proliferation of neurofibromas and other types of tumors. The disorder manifests itself as autosomal dominant, with hereditary neurocutaneous lesions, developmental disorders of the skeletal system, nervous system and skin [2]. The incidence of type 1 neurofibromatosis is 1: 2000-3500, and prevalence of 1:4-5000 with no significant difference between men and women and with wide phenotypic variability [3, 4].

Type 1 neurofibromatosis is most commonly diagnosed clinically. The diagnosis of von Recklinghausen's disease is made by the presence of at least two or more of the following clinical signs: coffee-colored patches over the body, (café au lait macules), axillary or inguinal freckles, onset of neurofibroma, optic gliomas, onset of hamartomas on the iris-lich nodules, disorders of the skeletal system and family history [5]. A rare manifestation of Von Recklinghausen's disease is the occurrence of intestinal neurofibromas, which are indirectly detected, mainly through bleeding from the digestive tract, or as a cause of anemia in patients, or existence of other intestinal disorders like intussusception in patients who either have or have no other clinical manifestations of neurofibromatosis [6-8].

Case report

A 69 year old patient was admitted to hospital for anal bleeding and short-term loss of consciousness for about 2 minutes. The patient gave the information about persistent he-

adaches for which she was taking ibuprofen.

On admission, the patient was consciously oriented, with pale skin and mucous membranes, with noticeable scoliosis of the thoracic segment of the spinal column. On the skin of the face and abdomen, there were more tumefactions (plexiform neuroblastomas) ranging from the size of a pea grain to the size of an egg. There were also present white coffee-colored stains (café au lait macules) over 15mm in diameter on the skin of the thorax and the abdomen, the largest of which was positioned paraumbilically, 50x30mm in size. Abdominal and thorax skin freckles were present, being most visible in the inguinal region. Based on clinical findings, the clinical presentation indicated type 1 neurofibromatosis (von Recklinghausen's disease).

There was an incision at the midline of the lower abdomen for which anamnestic information was obtained that it was made during hysterectomy performed because of a benign uterine tumor (Figure 1).

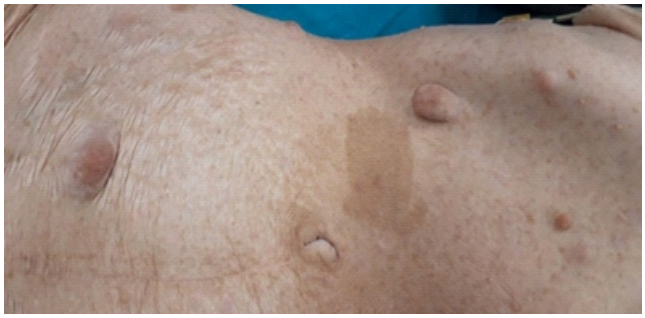

Figure 1. Plexiform neuroblastomas, café au lait macules, and freckles of the skin on the abdomen.

On the left side of the thorax, a 150x50x90mm tumor (neurofibroma) was observed, and it was attached to the anterolateral segment of the left rib arch (Figure 2).

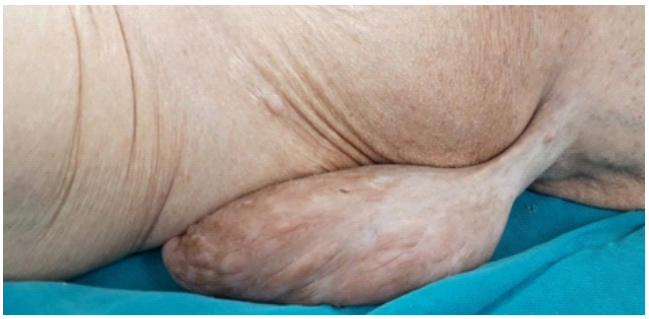

Figure 2. A large tumor attached to the left side of the thorax

Laboratory analyzes on admission: RBC 2.36x10^{12}/L - Low value (L); HGB 73g/L (L); HCT 0.21 (L); PLT 125x10^{9}/L (L); WBC 8.3x10^{9}/L. Blood biochemical analyzes were within the reference values except for total proteins 55.7g/L (L); serum albumins 34g/L (L); HDL 0.85 (L); total cholesterol 2.82g/L (L), and little elevated serum glucose level of 7.0mmol/L and serum urea level of 9,9mmol/L.

The patient underwent proximal endoscopy (esophagogastroduodenoscopy) which showed a normal finding, with no signs of bleeding. Colonoscopy showed black content from the rectum to cecum. The sigmoidal segment of the colon was compressed from the outside, with the presence of three polyps in the lumen of intestine. No active bleeding was observed colonoscopically. The finding at the terminal ileum was within the normal limits.

Computed tomography (CT) angiography of a mesenteric artery and magnetic resonance imaging (MRI) showed the presence of a tumor mass originating from the anterolateral segment of the thorax, with vascularization that originated from the intercostal arteries. In the small pelvis, a lobulated heterodense lesion with the diameter of 73x65mm was present, which shows a marginal enhancement to the contrast application. Similar changes were observed in the right iliac region with the diameter of 9x40mm, and another one dorsally at the level of the lumbosacral junction with the diameter of 14x26mm. The presence of a fistula between the colon and the tumor mass in the pelvis (Figure 3) was suspected.

The patient was referred to nuclear medicine department for the GIBS. The procedure was done by protocol recommended by The Society of Nuclear Medicine and Molecular Imaging (SNMMI) [9]. Technetium-99m-labeled autologous red blood cells (^{99m}Tc-RBC) was used with in vivo labeling. The administered activity of ^{99m}Tc-RBC was 555MBq. Scintigraphy was done on dual head gamma camera (Siemens e-cam). The patient was in supine position and the detector of gamma camera was positioned over the abdomen and pelvis. The matrix of 128x128 was used. Nuclear angioscintigrams were first obtained, with the frame rate of 2 seconds per frame for 60 seconds. Immediately after angioscintigrams, the dynamic study was performed in the same projection with frame rate of one frame per 30 seconds for the total duration of 45 minutes.

Scintigraphy showed radiopharmaceutical activity at the level of the jejunum, in the extracorporeal tumor and its petiole through which it was connected, taking arterial blood supply probably from the intercostal arteries, but also at the level of the descending and the rectosigmoidal colon (Figure 4). The described activity indicated active intraluminal hemorrhage in the jejunum, which was going downwards to the descending and rectosigmoidal colon. An extracorporeal tumor was presented as a hypervascularized lesion.

Dynamic scintigrams detected hemorrhage in the small intestine, descending, sigmoidal and rectal region of the large intestine (Figure 5).

The patient was then referred to surgery department, where she was underwent surgical intervention. After opening the abdomen for exploration, there were two tumor sites on the small intestine, the first at 40cm and the second at 100cm from the duodenojejunal junction (from the ligamentum Treitz). On jejunum serosa, there were more than 10 nodules up to 2mm in size (biopsy taken). The first lesion of 4cm in size was resected, with an end-to-end anastomosis. A second lesion with similar macroscopic features, 10cm in diameter, partially fixed on the peritoneum of the pelvis and the anterior wall of the rectal part of the large intestine, was partially resected and released, when terminal anastomosis was done (Figure 5). Exploration of the abdomen showed no

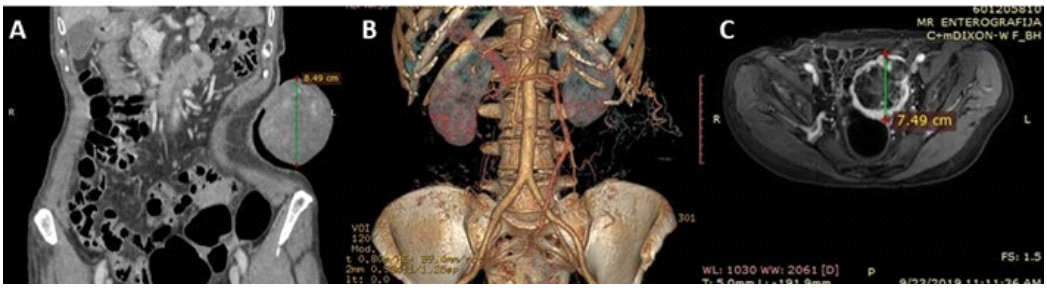

Figure 3. A: coronal section on MSCT with the visualization of the extracorporeal tumor mass; B: CT angiogram with no sign of hemorrhage; C: MRI section of the pelvis;

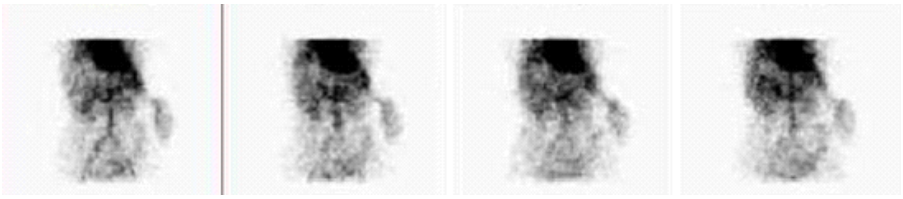

Figure 4. Angioscintigrams with the signs of hemorrhage in the projection of the small intestine and extracorporeal tumor presented as a hypervascularized lesion.

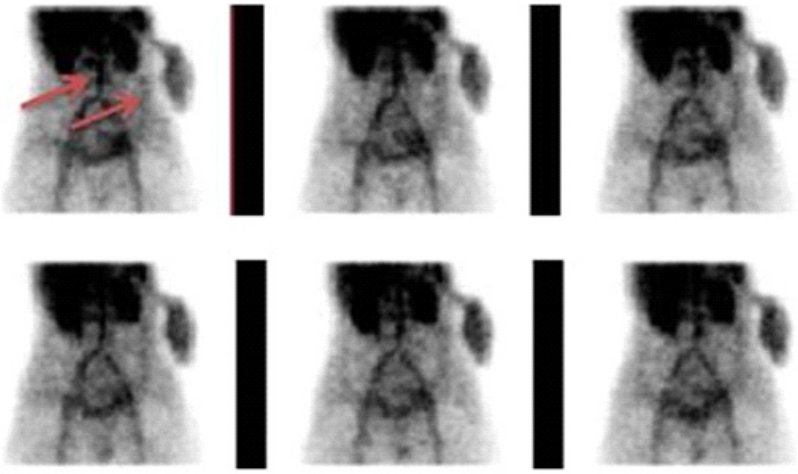

Figure 5. Dynamic scintigram of the abdomen. Arrows indicate the signs of intestinal hemorrhage in the small and large intestine.

other pathological changes. The postoperative course was uneventful. The histopathological diagnosis of the tumor in the jejunum, descending by the descending colon and positioned in the small pelvis where it partially compressed the sigmoidal part of the colon, was neurofibroma (Figure 6).

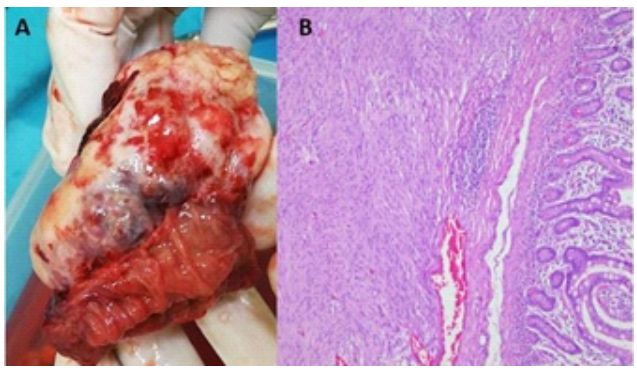

Figure 6. A. Surgical treatment of small intestine neurofibroma; B. histopathological finding with proliferation of spindle cells expanding to the submucosa and leading to the separation of the jejunal mucosa.

Discussion

Type 1 neurofibromatosis is a hereditary disorder with 100% penetration, regardless of gender. The disorder is reflected through the appearance of benign tumors, composed of peripheral nerve elements due to disruption of neurofibromin synthesis, caused by a gene disorder for its production located on the 17th chromosome [10, 11]. Involvement of the gastrointestinal tract in von Recklinghausen's disease is reported in approximately 5%-25% of patients [12, 13]. Neurofibromatosis of the gastrointestinal tract originates mainly from the Meissner's or Auerbachi's plexus. The Meissner's plexus produces neurofibromas originating from the submucosa, while those developing in the tunica muscularis originate from the Auerbachi's plexus [14]. The number of neurofibromas in digestive tract varies from a solitary tumor to dozens, even hundreds of tumor changes, which mostly affect the jejunum, ileum and the large intestine. Most of these changes have sessile presentations, some of which may

have ulceration that is macroscopically very irregular in shape. In addition, type 1 neurofibromatosis may be associated with the existence of other gastrointestinal tract tumors, such as leiomyomas, carcinoids, somatostatinomas, sarcomas and pancreatic adenocarcinomas [15].

The clinical picture of the presence of neurofibromatosis type 1 in the gastrointestinal tract depends on the position, size and number of lesions. Abdominal colic, intussusception, jaundice anemia due to occult hemorrhage, or clinical picture of active intestinal hemorrhage followed by consequent anemia, are most common [16]. There is a case reported with fatal retroperitoneal hemorrhage caused by neurofibromatosis that shows that patients with neurofibromatosis might develop spontaneous life-threatening bleeding from retroperitoneal located lesions [17]. Detection of small intestinal neurofibroma is difficult and is mainly detected during surgery due to the presence of intestinal intussusception or dysfunction of the small intestine. Radiological diagnostic methods may differentially diagnose the existence of lymphoma, carcinoids or Crohn's disease [18]. In patients whose clinical picture corresponds to the existence of Von Recklinghausen's disease, with the signs of active anal bleeding, the methods of choice for detecting the origin of active bleeding are CT angiography of the mesenteric artery or radionuclide diagnostics, which involves the detection of intestinal bleeding with 99metastable technetium labeled erythrocytes [19]. Nuclear medicine detection of intestinal bleeding is a method that allows the detection of bleeding volume of 0.04-0.2mL/min, (reported minimum bleeding rate of 0.04mL/min [20]), with sensitivity of 95%, specificity of 93% and accuracy of 94% [21, 22]. Some authors have published papers for GIBS with less specificity, which is probably due to the lack of the gold standard or incorrect selection of patients for examination [8]. Regarding GIBS in the planning of surgery after bleeding detection, the author's opinions differ, from those who place significant importance on surgery planning, to those who consider GIBS to be an irrelevant method before performing surgery in the sense of surgical approach planning [23, 24]. This kind of conclusion was made because the published studies were simply not focused on the evaluation of GIBS in the planning of surgical approach after intestinal bleeding was detected. Another reason for this opinion was lack of the unification of methodology in terms of using single photon emission tomography (SPET) or SPET/CT methodological approach instead of only planar techniques for both, detecting intestinal bleeding and its site of origin [25]. Single photon emission tomography methodology was described as useful in patients with equivocal planar findings or in patients with slow gastrointestinal bleeding [26, 27].

Although GIBS is not exact method to identify the bleeding and it is used more likely to point the surgeon to the most possible bleeding site, in this specific and rare case of intestinal neurofibroma originating from the jejunum and active bleeding from both tumors, GIBS has proven to be sensitive and specific both in terms of detecting the existence of bleeding in digestive tract and as a reliable localization tool for the origin of bleeding.

In conclusion, erythrocyte labeled scintigraphy is a significant, sensitive and specific method for detecting intestinal bleeding in the case of Von Recklinghausen disease and suspected bleeding from intestinally positioned neurofibromas if the bleeding is larger of 0.04mL/min. In the current case, GIBS showed active bleeding in neurofibromas in the jejunum, resulting in clinically evident rectal bleeding. In the described case, this approach enabled both the detection of bleeding and localization of the bleeding site as well as facilitated the pre-surgical treatment planning.

Bibliography

1. Williams VC, Lucas J, Babcock MA et al. Neurofibromatosis type 1 revisited. *Pediatrics* 2009; 123(1): 124-33.
2. Karaconji T, Whist E, Jamieson RV et al. Neurofibromatosis Type 1: Review and Update on Emerging Therapies. *Asia Pac J Ophthalmol (Phila)* 2019; 8(1): 62-72.
3. Evans DG, Howard E, Giblin C et al. Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. *Am J Med Genet* 2010; 152: 327-32.
4. Agaimy A, Vassos N Croner RS. Gastrointestinal manifestations of neurofibromatosis type 1 (Recklinghausen's disease): clinicopathological spectrum with pathogenetic considerations. *Int J Clin Exp Pathol* 2012; 5(9): 852-62.
5. Rosser T. Neurocutaneous Disorders. Continuum (MinneapMinn). *Child Neurology* 2018; 24: 96-129.
6. Al-Harake A, Chour M, Al Beteddini OS. Solitary intestinal neurofibroma with no associated systemic syndromes causing intussusception: Case report and literature review. *Int J Surg Case Rep* 2013; 4(7): 629-32.
7. Ahn S, Chung CS, Kim KM. Neurofibroma of the Colon: A Diagnostic Mimicker of Gastrointestinal Stromal Tumor. *Case Rep Gastroenterol* 2016; 10(3): 674-8.
8. Hahn JS, Chung JB, Han SH et al. Intestinal neurofibromatosis in von Recklinghausen's disease: presenting as chronic anemia due to recurrent intestinal hemorrhage. *Korean J Intern Med* 1992; 7(2): 137-42.
9. Dam HQ, Brandon DC, Grantham VV et al. The SNMMI procedure standard/EANM practice guideline for gastrointestinal bleeding scintigraphy 2.0. *J Nucl Med Technol* 2014; 42(4): 308-17.
10. Ricardi VM, Eichner JE. Neurofibromatosis: phenotype, natural history and pathogenesis. Baltimore: *Johns Hopkins University Press*; 1986.
11. Longo DL, Kasper DL, Jameson JL et al. *Harrison's principles of internal medicine*. 18th *edn*. New York: McGraw-Hill; 2012.
12. Lefere I, Dalle I, Thieren H et al. Diffuse intestinal ganglioneuromatosis of the ileum. *J Belge de Radiologie: Belgisch Tijdschriftvoor Radiologi* 2012; 95: 152-3.
13. Basile U, Cavallaro G, Polistena A et al. Gastrointestinal and retroperitoneal manifestations of type 1 neurofibromatosis. *J Gastrointest Surg* 2010; 14: 186-94.
14. Boldorini R, Tosoni A, Leutner M et al. Multiple small intestinal stromal tumours in a patient with previously unrecognized neurofibromatosis type 1: immunohistochemical and ultrastructural evaluation. *Pathology* 2001; 33: 390-5.
15. Pinsk I, Dukhno O, Ovnat A, Levy I. Gastrointestinal complications of von Recklinghausen's disease: two case reports and a review of the literature. *Scand J Gastroenterol* 2003; 38: 1275-8.
16. Carter JE, Laurini JA. Isolated intestinal neurofibromatous proliferations in the absence of associated systemic syndromes. *World J Gastroenterol* 2008; 14(2): 6569-71.
17. Moerbeek PR, van Buijtenen JM, van den Heuvel B et al. Fatal retroperitoneal bleeding caused by neurofibromatosis: a case report and review of the literature. *Case Rep Med* 2015; 2015: 965704.
18. Tobler A, Maurer R, Klaiber C. Stenosingganglioneuromatosis of the small intestine with ileus and ileal rupture. *Schweiz Med Wochenschr* 1981; 111: 684-8.
19. Abramson LP, Orkin BA, Schwartz AM. Isolated colonic neurofibroma manifested by massive lower gastrointestinal bleeding and intussusception. *South Med J* 1997; 90: 952-4.
20. Mariani G, Pauwels EKJ, AlSharif A et al. Radionuclide evaluation of the

lower gastrointestinal tract. *J Nucl Med Off Publ Soc Nucl Med* 2008; 49(5): 776-87.
21. Middleton ML, Strober MD. Planar scintigraphic imaging of the gastrointestinal tract in clinical practice. *Semin Nucl Med* 2012; 42(1): 33-40.
22. Allen TW, Tulchinsky M. Nuclear medicine tests for acute gastrointestinal conditions. *Semin Nucl Med* 2013; 43(2): 88-101.
23. Gunderman R, Leef J, Ong K et al. Scintigraphic screening prior to visceral arteriography in acute lower gastrointestinal bleeding. *J Nucl Med* 1998; 39: 1081-3.
24. Dusold R, Burke K, Carpentier W et al. The accuracy of technetium-99m-labeled red cell scintigraphy in localizing gastrointestinal bleeding. *Am J Gastroenterol* 1994; 89: 345-8.
25. Hunter JM, Pezim ME. Limited value of technetium 99m-labeled red cell scintigraphy in localization of lower gastrointestinal bleeding. *Am J Surg* 1990; 159: 504-6.
26. Grady E. Gastrointestinal Bleeding Scintigraphy in the Early 21st Century. *J Nucl Med* 2016; 57: 252-9.
27. Bentley BS, Tulchinsky M. SPECT/CT helps in localization and guiding management of small bowel gastrointestinal hemorrhage. *Clin Nucl Med* 2014; 39: 94-6.