

CASE REPORT

Open Access



^{18}F -FDG PET/CT findings in nevoid basal cell carcinoma syndrome: a systematic review and a new case report

Jing Zhang¹, Yonghong Zhang², Yumeng Jiang¹, Aodi Xu¹ and Yanli Wang^{1*}

Abstract

Background To demonstrate and analyze the ^{18}F -FDG positron emission tomography/computed tomography (PET/CT) findings in this rare nevoid basal cell carcinoma syndrome (NBCCS).

Case presentation A 71-year-old woman with the left invasive breast cancer was treated with hormone therapy for six months and underwent the ^{18}F -FDG PET/CT examination for efficacy evaluation. ^{18}F -FDG PET/CT revealed the improvement after treatment and other unexpected findings, including multiple nodules on the skin with ^{18}F -FDG uptake, bone expansion of cystic lesions in the bilateral ribs, ectopic calcifications and dilated right ureter. She had no known family history. Then, the patient underwent surgical excision of the all skin nodules and the postoperative pathology were multiple basal cell carcinomas. Finally, the comprehensive diagnosis of NBCCS was made. The patient was still in follow-up. Additionally, we have summarized the reported cases ($n = 3$) with ^{18}F -FDG PET/CT from the literature.

Conclusions It is important to recognize this syndrome on ^{18}F -FDG PET/CT because of different diagnoses and therapeutic consequences.

Keywords ^{18}F -FDG PET/CT, Nevoid basal cell carcinoma syndrome, Gorlin-Goltz syndrome, Basal cell nevus syndrome, Breast cancer, Case report

Background

Nevoid basal cell carcinoma syndrome (NBCCS), also known as Gorlin-Goltz syndrome (GGS) and Basal cell nevus syndrome (BCNS), is a rare autosomal dominantly inherited disorder, which is characterized by a wide range of developmental abnormalities and the susceptibility to multiple neoplasms [1–3]. The main clinical presentations include multiple basal cell carcinomas, odontogenic

keratocysts, palmoplantar pits, ectopic calcification, skeletal abnormalities and the increased risk of medulloblastoma. Lack of awareness of this syndrome among radiologists and clinicians have led to inappropriate management and treatment for this particular group. A literature reported a case of NBCCS who was diagnosed after developing the fifth type of cancer [4].

Up to now, the majority of published articles reported clinical presentations and conventional imaging manifestations, including X-ray plain film, computed tomography (CT) and magnetic resonance imaging (MRI). Compared to conventional imaging, ^{18}F -FDG positron emission tomography/computed tomography (PET/CT) could perform whole-body scan and detect more evidences to support the diagnosis of NBCCS. Additionally, as a non-invasive imaging technique, ^{18}F -FDG PET/CT

*Correspondence:

Yanli Wang
wangyanli1105@163.com

¹ Department of PET/CT, Qingdao Central Hospital, No 127. SiLiu Nan Street, ShanDong Province, Qingdao City 266042, China

² Department of Burn and Plastic Surgery, Qingdao Central Hospital, ShanDong Province, Qingdao 266042, China



© The Author(s) 2024. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

could provide both anatomical and molecular metabolic information. However, the imaging characteristics of NBCCS on ^{18}F -FDG PET/CT have rarely been described. We reviewed previous studies and found only three case reports demonstrating ^{18}F -FDG PET/CT manifestations of NBCCS [5–7].

We recently encountered a case of NBCCS who was diagnosed at the time of ^{18}F -FDG PET/CT examination for efficacy evaluation of the left invasive breast cancer. The purpose of this study was to demonstrate the ^{18}F -FDG PET/CT findings of NBCCS and raise awareness of this syndrome.

Case presentation

A 71-year-old women, with a biopsy-proven case of the left invasive breast cancer, received the hormone therapy (exemestane, 25 mg/day) for six months. Patient self-reported a history of resection for multiple basal cell carcinomas of the skin and received radiation therapy for twenty years. Enlarged skin nodules with itching symptom in the last five years. She denied fever, weight loss and other obvious discomfort symptoms. Laboratory result was notable for increased white cell counts 651.93/uL (reference range, 0.00–25.00/uL) in the routine urine testing. The levels of all tumor markers, including carcinogenic embryonic antigen (CEA), cancer antigen153 (CA153) and cancer antigen 125 (CA125), were within the normal range. ^{18}F -FDG PET/CT revealed that the breast lesion was significantly reduced in volume and slightly increased in ^{18}F -FDG metabolism [Maximum standardized uptake value (SUVmax), 1.6] (Fig. 1), which

indicated the improvement after treatment. There were multiple black and irregular nodules on patient's head (Fig. 2A), face (Fig. 2A) and anterior chest skin (Fig. 2D). These nodules exhibited different levels of ^{18}F -FDG uptake on PET/CT (Fig. 2B-C and Fig. 2E-F). The highest level of ^{18}F -FDG uptake was found on patient's face skin (SUVmax, 6.2). Meanwhile, the bilateral ribs showed bone expansion of cystic lesions and mild thickening of the bone cortex with increased ^{18}F -FDG metabolism (SUVmax, 3.9) on PET/CT (Fig. 3A,B). When we reviewed her chest CT images from two years ago, the bilateral ribs have developed cystic changes (Fig. 3C). Currently, the volume slightly increased compared by before. Other interesting findings included ectopic calcifications in the falx cerebri (Fig. 3D), tentorium cerebellum (Fig. 3D) and left ovary (Fig. 3E). There was no significant abnormal ^{18}F -FDG metabolism in the region of left ovary (Fig. 3F). The right ureter was dilated (Fig. 3E,F), which was related with history of pyelonephritis. The patient underwent surgical excision of the all skin nodules. The postoperative pathology were multiple basal cell carcinomas. Pathologic findings of breast cancer and basal cell carcinomas were shown in the Fig. 4A and B, respectively. Finally, comprehensive diagnosis of NBCCS was made. The patient was still in follow-up.

Then, we summarized the prior reported cases of NBCCS with ^{18}F -FDG PET/CT presentations. In our review, there were 4 cases in total including our case. Pachowicz et al. [5] reported a 51-year-old patient had multifocal skin basal cell carcinomas. ^{18}F -FDG PET/CT revealed complex rib anomalies, scoliosis with vertebral

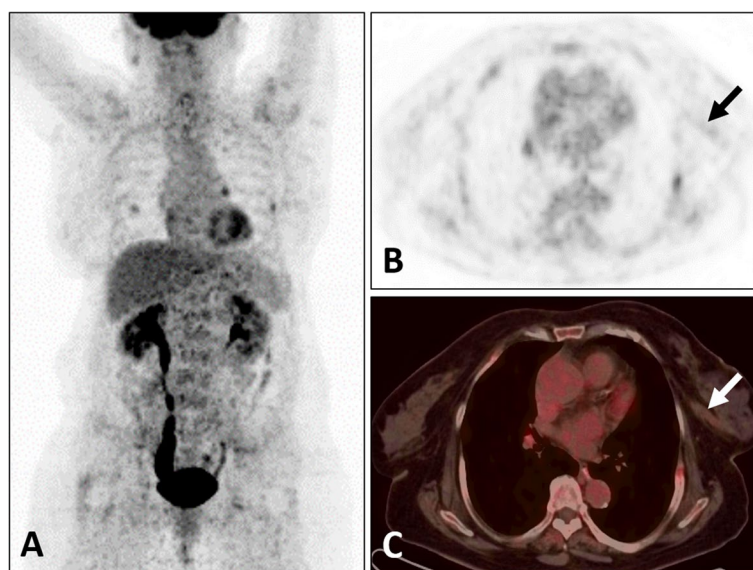


Fig. 1 Nevoid basal cell carcinoma syndrome (NBCCS) in a 71-year-old woman with the left invasive breast cancer. The lesion in the left breast (arrow) appeared as strip-like with mildly elevated metabolism of ^{18}F -FDG (A: MIP; B: PET; C: PET/CT)

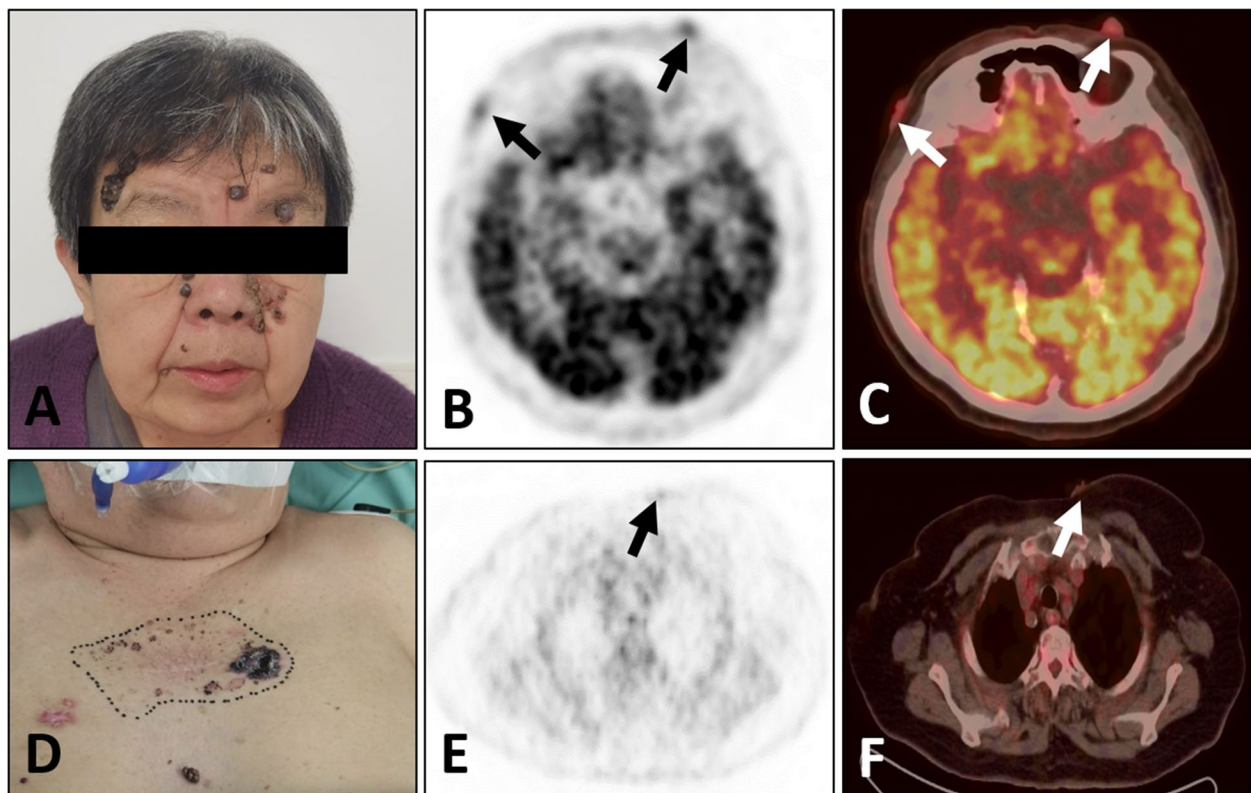


Fig. 2 Nevoid basal cell carcinoma syndrome (NBCCS) in a 71-year-old woman with the left invasive breast cancer. There were multiple black and irregular nodules on the head, face and chest wall skin (A, D). These nodules (arrows) exhibited the different levels of ^{18}F -FDG uptake on PET/CT (B and E: PET; C and F: PET/CT)

malformations and cysts of jaw. But no ^{18}F -FDG avid areas were observed on PET/CT. Yin et al. [6] reported an 18-year-old woman had a surgical history of removing multiple odontogenic cysts. ^{18}F -FDG PET/CT showed a cyst in the right maxilla with ^{18}F -FDG uptake. MRI of the pelvis demonstrated a large solid tumor of the right ovary and postoperative pathology confirmed the benign ovarian fibroma. Reaz et al. [7] reported a 20-year-old woman underwent a surgery of odontogenic keratocysts. There was a hyperactive mass in the left ventricle and no other hypermetabolic area on whole-body ^{18}F -FDG PET/CT. Our case reported multiple basal cell carcinomas with ^{18}F -FDG uptake, bone expansion of cystic lesions in the bilateral ribs and ectopic calcifications (the falx cerebri, tentorium cerebellum and left ovary). And these findings were found during the efficacy evaluation of breast cancer. The ^{18}F -FDG PET/CT findings of all cases were detailed in Table 1.

Discussion and conclusions

NBCCS is a rare autosomal dominantly inherited disorder and presents as multisystem abnormalities. This disease has the estimated prevalence of 1/57000 to 1/256000

and both sexes are equally affected [8]. The patched-1 (PTCH1) gene, an onco-suppressor gene that maps at 9q22.3 region, is the major causative gene of NBCCS, which involves in the hedgehog signaling pathway [9, 10]. The mutation is transmitted in an autosomal dominant inheritance from parents to their children. However, 35% to 50% of NBCCS are spontaneous mutations and without family history [10].

The diagnostic criteria for NBCCS were first proposed by Evans et al. in 1993 [11]. After the reviewed and revised by Kimonis et al. in 1997 [12], Kimonis et al. [13] in 2004 and Bree et al. in 2011 [14]. A positive diagnosis was established by the presence of one major criterion and genetic confirmation or by two major criteria or by one major and two minor criteria. The major diagnostic criteria would include multiple basal cell carcinomas, odontogenic keratocyst of the jaw, palmar pitting, calcification of the falx cerebri, medulloblastoma and first-degree relatives with NBCCS. And the minor diagnostic criteria would include rib abnormalities, other skeletal malformations and radiologic changes, macrocephaly, lip palate, cardiac or ovarian fibroma, lymphomesenteric cysts and ocular abnormalities. Although the patient in

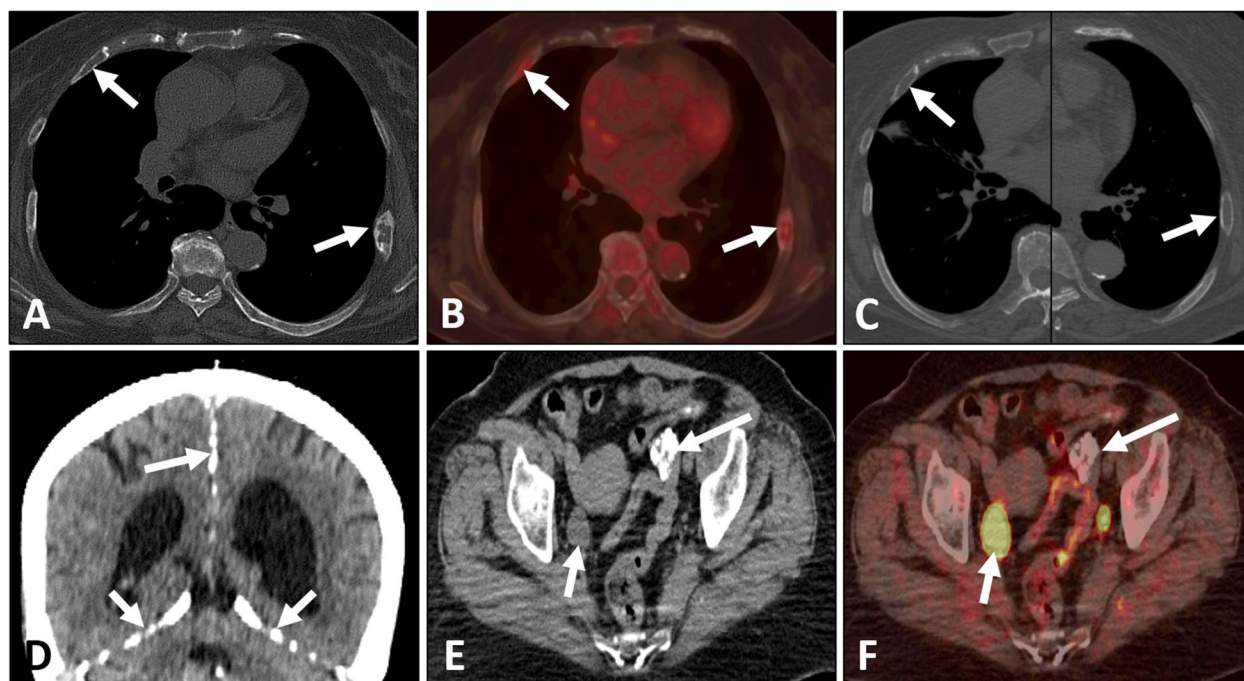


Fig. 3 Nevoid basal cell carcinoma syndrome (NBCCS) in a 71-year-old woman with the left invasive breast cancer. The bilateral ribs (arrows) showed bone expansion of cystic lesions and mild thickening of the bone cortex with increased ^{18}F -FDG uptake on PET/CT (**A**: PET; **B**: PET/CT). Two years ago, the patient's chest CT images showed the bilateral ribs (arrows) had developed cystic changes (**C**: CT). The falx cerebri (long arrow) and tentorium cerebellum (short arrows) were accompanied with multiple calcifications (**D**: CT). The left ovary (long arrow) also developed multiple calcifications without ^{18}F -FDG uptake (**E**: CT; **F**: PET/CT). The right ureter (short arrow) was dilated (**E**: CT; **F**: PET/CT)

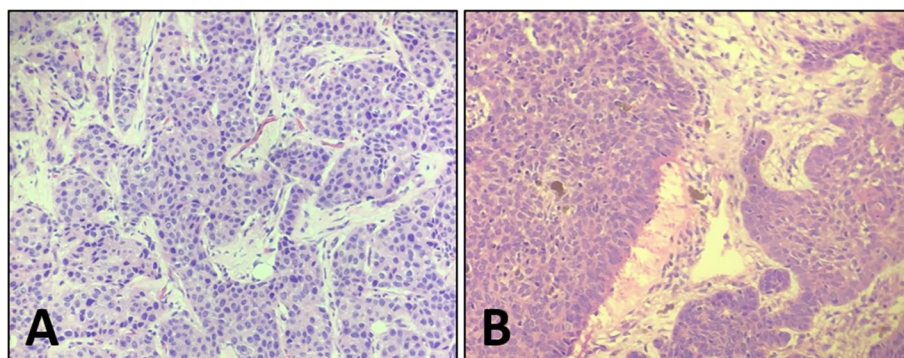


Fig. 4 Puncture biopsy of left breast showed invasive carcinoma with histologic grade II. (**A**, hematoxylin–eosin stain $\times 20$). Pathologic findings of the excised skin lesions showed basal cell carcinomas with breakdown and abscess formation, infiltrating the dermis (**B**, hematoxylin–eosin stain $\times 20$)

our report denied family history of NBCCS and did not get *PICHI* genetic testing, she had multiple basal cell carcinomas, ectopic calcifications and bilateral rib anomalies, which met the diagnostic criteria for NBCCS.

In previously published articles, the authors mostly reported the clinical presentations and conventional imaging manifestations [4, 15–20]. Figueira et al. [21] emphasized that it is essential for dental surgeons and

dermatologists to know the signs and symptoms of NBCCS, which is important for patients to get early diagnosis and more rational approach to the treatment. Compared to conventional imaging, PET/CT, as a whole-body examination, had the advantage to find more multisystem abnormalities to support the diagnosis of NBCCS. However, there were only three case reports based on PET/CT scans. Additionally, we

Table 1 The ^{18}F -FDG PET/CT findings in Nevoid basal cell carcinoma syndrome (NBCCS)

	Pachowicz et al. [5]	Yin et al. [6]	Reaz et al. [7]	Present case
Multiple basal cell carcinomas	former	-	-	+
Odontogenic keratocyst	+	+	former	-
Skeletal anomalies	+	-	-	+
Ectopic calcification	-	-	-	+
Cardiac fibroma	-	-	+	-
Ovarian fibroma	-	+	-	-
Breast cancer	-	-	-	+

+ Positive

-Negative

were the first to report that breast cancer patient with NBCCS on PET/CT.

Basal cell carcinoma is a relatively inert primary cutaneous neoplasm, which usually invades the local skin and adjacent structures but rarely metastasizes far away. It has also been associated with certain syndromes, the NBCCS being the most common [22]. Ayala et al. [23] held the view that ^{18}F -FDG PET/CT may be helpful in the management of patients with advanced basal cell carcinoma. Because it not only could assess the location and extent of skin lesions, but also early detect metastases [23, 24]. PET/CT be able to provide more information to clinicians to make therapeutic decisions. The patient in our report had the history of multiple basal cell carcinomas and left invasive breast cancer. If radiologists were aware of the link between various diseases, they would make the correct diagnosis of NBCCS and provide reasonable advice to clinicians. From a prognostic standpoint, early diagnosis and appropriate treatment are critical. If diagnosed, lifelong care with interdisciplinary medical collaboration is necessary [25].

In the case of presenting skin lesions, identification of cutaneous metastases originating from breast cancer and primary basal cell carcinomas was important for the patient's therapeutic choices. Metastasis from internal malignant tumors to the skin was rare, with an incidence of 0.7–10%. Of all malignant tumors, breast cancer had the highest incidence of cutaneous metastases [26, 27]. Lookingbill et al. [28] reported that 237 of 992 breast cancer patients (23.8%) had cutaneous metastases, which could occur via lymphatic or bloodstream transmission and were most common in the head, neck and trunk. We should be vigilant for non-healing ulcers, persistently hardening erythema and newly developed skin nodules [28, 29]. Previous studies suggested that these cutaneous metastatic lesions exhibit varying degrees of increased ^{18}F -FDG metabolism [26, 27, 30]. In our case, the level of ^{18}F -FDG

metabolism in the treated breast cancer was lower than skin lesions, and no definite metastatic lesion was found at other site. Clinically, the levels of tumor markers (CEA, CA153 and CA125) were within the normal range. Therefore, we suspected that the skin lesions were the other primary tumors. Of course, pathological examination is necessary to identify primary and metastatic lesions. In addition, we also need to identify skin changes associated with breast cancer treatment. Skin toxicity changes associated with immunotherapy for renal cancer have been reported in the past, which closely correlate with the treatment history. The associated skin and subcutaneous lesions would subside after discontinuation of the drug [31].

In conclusion, NBCCS is a relatively rare syndrome, which have the features of developmental abnormalities and tumor susceptibility. Compared to conventional imaging, ^{18}F -FDG PET/CT has more advantages in diagnosing of NBCCS. It is important to recognize this syndrome on ^{18}F -FDG PET/CT because of different diagnoses and therapeutic consequences.

Abbreviations

NBCCS	Nevoid basal cell carcinoma syndrome
GGs	Gorlin-Goltz syndrome
BCNS	Basal cell nevus syndrome
PET/CT	Positron emission tomography/computed tomography
CT	Computed tomography
MRI	Magnetic resonance imaging
SUVmax	Maximum standardized uptake value
CEA	Carcinogenic embryonic antigen
CA153	Cancer antigen153
CA125	Cancer antigen 125

Acknowledgements

The authors were grateful to and thank the patient for her cooperation in our study.

Authors' contributions

Jing Zhang wrote the main manuscript text. Yonghong Zhang, Yumeng Jiang and Aodi Xu conducted data collection and analysis. All authors reviewed the manuscript. Yanli Wang revised and approved the final manuscript.

Funding

This work was supported by Qingdao Key Health Discipline Development Fund.

Availability of data and materials

The datasets generated during the current study were available from the corresponding author on reasonable request.

Declarations**Ethics approval and consent to participate**

This study was performed in line with the principles of the Declaration of Helsinki. And this was an observational study. The Medical Ethics Committee of the Affiliated Qingdao Central Hospital of Qingdao University has confirmed that no ethical approval is required.

Consent to publication

The patient gave her written informed consent for the publication of any identifying information/images in this case report.

Competing interests

The authors declare no competing interests.

Received: 17 August 2023 Accepted: 15 May 2024

Published online: 28 May 2024

References

- Hasan A, Akintola D. An Update of Gorlin-Goltz Syndrome. *Prim Dent J*. 2018;7(3):38–41.
- Verkouteren BJA, Cosgun B, Reinders MGHC, Kessler PAWK, Vermeulen RJ, Klaassens M, Lambrechts S, van Rheenen JR, van Geel M, Vreeburg M, Mosterd K. A guideline for the clinical management of basal cell naevus syndrome (Gorlin-Goltz syndrome). *Br J Dermatol*. 2022;186(2):215–26.
- Fernández LT, Ocampo-Garza SS, Elizondo-Riojas G, Ocampo-Candiani J. Basal cell nevus syndrome: an update on clinical findings. *Int J Dermatol*. 2022;61(9):1047–55.
- Katayama D, Inoue A, Kayatani R, Urabe K, Suzuki R, Takitani K, Yoshida M, Kato M, Ashida A. A Case of Gorlin-Goltz Syndrome Without the Characteristic Physical Features That Was Diagnosed After the Development of a Fifth Cancer. *J Pediatr Hematol Oncol*. 2022;44(4):e869–71.
- Pachowicz M, Staskiewicz G, Opielak G, Scibisz-Dziedzic K, Chrapko B. Complex rib anomalies in patient undergoing PET/CT study - a case report. *Nucl Med Rev Cent East Eur*. 2017;20(1):64–5.
- Yin H, Shi H. Fluorine 18 Fluorodeoxyglucose PET/CT Findings in Gorlin-Goltz Syndrome. *Radiology*. 2021;300(2):288.
- Reaz S, Sammi S, Gholkar G. A rare case of cardiac fibroma diagnosis in Gorlin-Goltz syndrome with information on management. *Future Cardiol*. 2022;18(7):561–7.
- Lo ML. Nevoid basal cell carcinoma syndrome (Gorlin syndrome). *Orphanet J Rare Dis*. 2008;3:32.
- Beltrami B, Prada E, Tolva G, Scuvera G, Silipigni R, Graziani D, Bulfamante G, Gervasini C, Marchisio P, Milani D. Unexpected phenotype in a frameshift mutation of PTCH1. *Mol Genet Genomic Med*. 2020;8(1):e987.
- Pazdera J, Santava A, Kolar Z. Gorlin-Goltz syndrome with familial manifestation. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2022;166(1):112–6.
- Evans DG, Ladusans EJ, Rimmer S, Burnell LD, Thakker N, Farndon PA. Complications of the naevoid basal cell carcinoma syndrome: results of a population based study. *J Med Genet*. 1993;30(6):460–4.
- Kimonis VE, Goldstein AM, Pastakia B, Yang ML, Kase R, DiGiovanna JJ, Bale AE, Bale SJ. Clinical manifestations in 105 persons with nevoid basal cell carcinoma syndrome. *Am J Med Genet*. 1997;69(3):299–308.
- Kimonis VE, Mehta SG, DiGiovanna JJ, Bale SJ, Pastakia B. Radiological features in 82 patients with nevoid basal cell carcinoma (NBCC or Gorlin) syndrome. *Genet Med*. 2004;6(6):495–502.
- Bree AF, Shah MR, BCNS Colloquium Gr. Consensus statement from the first international colloquium on basal cell nevus syndrome (BCNS). *Am J Med Genet A*. 2011;155A(9):2091–7.
- Hino S, Tanaka H, Hamakawa H. Multiple jaw cysts and ectopic calcification. *BMJ Case Rep*. 2017;2017:bcr2017219344.
- Borghesi A, Nardi C, Giannitto C, Tironi A, Maroldi R, Di Bartolomeo F, Preda L. Odontogenic keratocyst: imaging features of a benign lesion with an aggressive behaviour. *Insights Imaging*. 2018;9(5):883–97.
- Kumar S, Eshanth R, Indiran V, Mariappan K, Maduraimuthu P. A rare association of Gorlin-Goltz syndrome. *Neurol India*. 2018;66(3):847–9.
- Moramarco A, Himmelblau E, Miraglia E, Mallone F, Roberti V, Franzone F, Iacovino C, Giustini S, Lambiase A. Ocular manifestations in Gorlin-Goltz syndrome. *Orphanet J Rare Dis*. 2019;14(1):218.
- Narang A, Maheshwari C, Aggarwal V, Bansal P, Singh P. Gorlin-Goltz Syndrome with Intracranial Meningioma: Case Report and Review of Literature. *World Neurosurg*. 2020;133:324–30.
- Singh RK, Mishra GV. Gorlin-Goltz syndrome without cutaneous manifestations. *Pan Afr Med J*. 2021;39:239.
- Figueira JA, Batista FRS, Rosso K, Veltrini VC, Pavan AJ. Delayed Diagnosis of Gorlin-Goltz Syndrome: The Importance of the Multidisciplinary Approach. *J Craniofac Surg*. 2018;29(6):e530–1.
- Baheti AD, Tirumani SH, Giardino A, Rosenthal MH, Tirumani H, Krajewski K, Ramaiya NH. Basal cell carcinoma: a comprehensive review for the radiologist. *AJR Am J Roentgenol*. 2015;204(2):W132–40.
- Ayala S, Perlaza P, Puig S, Prats E, Vidal-Sicart S. Usefulness of (18)F-FDG PET/CT in recurrent basal cell carcinoma: Report of a case. *Rev Esp Med Nucl Imagen Mol*. 2016;35(2):124–6.
- Pabst A, Klinghuber M, Müller G, Vandersee S, Werkmeister R. Extensive bony metastases from facial metatypical basal cell carcinoma: a case report. *Br J Oral Maxillofac Surg*. 2019;57(1):82–4.
- Bartoš V, Kullová M, Adamicová K, Paučinová I. Gorlin-Goltz syndrome. *Klin Onkol*. 2019;32(2):124–8.
- Borkar S, Pandit-Taskar N. F-18 FDG uptake in cutaneous metastases from breast cancer. *Clin Nucl Med*. 2008;33(7):488–9.
- Dave SR, Samuel TA, Pucar D, Savage N, Williams HT. FDG PET/CT in evaluation of unusual cutaneous manifestations of breast cancer. *Clin Nucl Med*. 2015;40(1):e63–7.
- Lookingbill DP, Spangler N, Sexton FM. Skin involvement as the presenting sign of internal carcinoma. A retrospective study of 7316 cancer patients. *J Am Acad Dermatol*. 1990;22(1):19–26.
- Rehman S, Naveed MA. Skin Metastasis in Breast Cancer Patients; a Case Series. *J Cancer Allied Spec*. 2020;6(1):307.
- Muzaffar M, Hassan A. 18F-FDG PET-CT in Cutaneous Metastases in Breast Carcinoma: An unusual presentation. *J Pak Med Assoc*. 2023;73((1(B))):433–4.
- T T, Goyal H, Singh H, Das CK, Sekar A, Kumar R. Nivolumab Immunotherapy-Related Skin Reactions Detected on 18F-FDG PET/CT in Renal Cell Cancer. *Clin Nucl Med*. 2022;47(7):e513–4.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.