THE RARITY AND COMPLEXITY OF GORLIN-GOLTZ SYNDROME: DIAGNOSTIC CRITERIA AND THERAPEUTIC LIMITATIONS IN A 50-YEAR-OLD PATIENT WITH MULTIPLE INOPERABLE BASAL CELL CARCINOMAS

DANIELA-VASILICA ȘERBAN*,**,***, DANIELA CRAINIC,**,***, ROXANA FERICEAN*,**,***, NINA IVANOVIC*,**,***, ANA OLIVIA TOMA*,**,***,

Summary

Gorlin-Goltz syndrome is a rare genetic disorder with autosomal dominant inheritance, characterized by an increased predisposition to develop multiple basal cell carcinomas, odontogenic cysts, and skeletal abnormalities. Diagnosis is based on specific clinical and genetic criteria, considering the phenotypic variability and progressive evolution of the disease.

We present the case of a 50-year-old patient diagnosed with Gorlin-Goltz syndrome, who developed multiple pigmented, ulcerated basal cell carcinomas predominantly located on the trunk and cephalic extremities, with advanced locoregional invasion.

The prognosis of these patients is reserved due to the high risk of recurrence and local invasion, as well as significant aesthetic and functional complications. The disease also has a major psychological and social impact, determined by the need for repeated interventions and impaired quality of life. This case highlights the importance of early diagnosis and a multidisciplinary approach.

Keywords: *Gorlin-Goltz syndrome, basal cell carci-noma, diagnostic criteria, PTCH1 mutation, multi-disciplinary approach.*

Received: 3.11.2025 *Accepted: 9.01.2026*

Introduction

Gorlin-Goltz syndrome, also known as Nevoid Basal Cell Carcinoma Syndrome (NBCCS), is a rare hereditary disorder characterized by a predisposition to develop multiple basal cell carcinomas, odontogenic cysts, and skeletal abnormalities. The disease follows an autosomal dominant pattern of inheritance, with variable penetrance and expressivity, even among members of the same family. The PTCH1 gene, located on the long arm of chromosome 9 (9q22.3–q31), functions as a tumor suppressor gene, playing an essential role in controlling cellular proliferation through the negative regulation of the Hedgehog signaling pathway.

The syndrome was first mentioned in the medical literature in 1894 by Jarisch and White, who described a case suggestive of this condition. Later, in 1960, Robert J. Gorlin and Robert W. Goltz defined it as a distinct entity, characterized by the classical triad of multiple nevoid basal cell

* Municipal Emergency Clinical Hospital, Department of Dermatology and Venereology, Timișoara.
** "Victor Babeș" University of Medicine and Pharmacy, Timișoara, Romania.
*** Morphological Skin Research Center / acronym MORPHODERM.

carcinomas, mandibular odontogenic cysts, and bifid ribs. The prevalence is estimated at 1 in 50,000 to 1 in 150,000 individuals, depending on the region, with no gender predilection (1).

Given the clinical heterogeneity and phenotypic variability of Gorlin-Goltz syndrome, specific diagnostic criteria have been established, integrating clinical, imaging, and genetic data to ensure a precise and standardized diagnostic approach.

Case presentation

We present the case of a 50-year-old male patient from a rural area, diagnosed in 2009 with Gorlin-Goltz syndrome.

The patient's medical history revealed the onset of the first cutaneous lesions during adolescence, initially presenting as erythematous papules that later became pigmented, predominantly located on the face and trunk. Over the course of the disease, the patient underwent multiple surgical excisions of tumoral lesions, which were histopathologically diagnosed as basal cell carcinomas (between 2005 and 2016), with frequent recurrences and the continuous development of new lesions.

In 2019, two courses of systemic chemotherapy (5-fluorouracil and cisplatin) were administered but discontinued at the patient's request due to intolerance. Subsequently, treatment with Vismodegib, a Hedgehog pathway inhibitor, was recommended.

In 2021, excision of a nodular basal cell carcinoma arising on a trichoepithelioma was performed at the level of the left auricular pavilion, followed in 2022 by excision of a local recurrence, which resulted in left peripheral facial paralysis.Thereafter, the patient had multiple ENT consultations due to persistent and progressively intensifying pain in the left hemicranium.

At the 2024 admission, clinical examination revealed a patient in slightly impaired general condition, known to have congenital hydrocephalus and grade II oligophrenia, underweight, with kyphoscoliosis and mild hypertelorism, reporting moderate-intensity pain localized to the left side of the head.

Local examination identified multiple pigmented, ulcerated tumoral lesions of variable shape and size (0.5–4 cm), predominantly located on the trunk and cephalic region.

At the level of the left temporal region, the absence of the left auricular pavilion and complete obstruction of the external auditory canal (EAC) were noted. Among the tumoral lesions, multiple postoperative scars with a depressed and partially retractile appearance were observed, corresponding to previous surgical excisions. Additionally, multiple punctate depressions were noted on the palms (Figure 1).

Given the increasing intensity of pain in the left hemicranium and the obstruction of the left external auditory canal (EAC), an ENT consultation was performed for local evaluation, and a craniofacial CT scan was recommended to assess the extent of the tumoral process.

Laboratory tests revealed elevated ESR (35 mm/h) and C-reactive protein (CRP = 21 mg/L) levels, along with increased GGT (117 U/L) and a marked vitamin D deficiency (11.5 ng/mL).

Nasal swab cultures identified the presence of methicillin-resistant *Staphylococcus aureus* (MRSA), while pharyngeal swabs showed multiple colonies of *Candida albicans*. The craniofacial CT scan revealed lateral ventricles positioned along the midline, markedly enlarged, consistent with hydrocephalus, without signs of ventricular exudation. Calcifications were observed at the level of the falx cerebri and bilateral tentorium cerebelli (Figure 2). In the right anterior temporal region, a well-outlined intracranial expansive process measuring approximately 38 Ṃ 38 mm was identified, exerting a compressive effect on the ipsilateral temporal horn.

At the level of the left external auditory canal (EAC), a complete obstruction was observed, caused by a heterogeneous, poorly defined tissue densification measuring approximately 23×23 mm.

Additionally, cystic lesions were identified at the level of the right mandibular ramus (30×13 mm) and the left paramedian maxilla, the latter showing included calcifications (17 Ṃ 16 mm) (Figure 3).

Dermatoscopic examination of the cutaneous lesions revealed maple leaf-like areas at the periphery of the tumors and radial projections

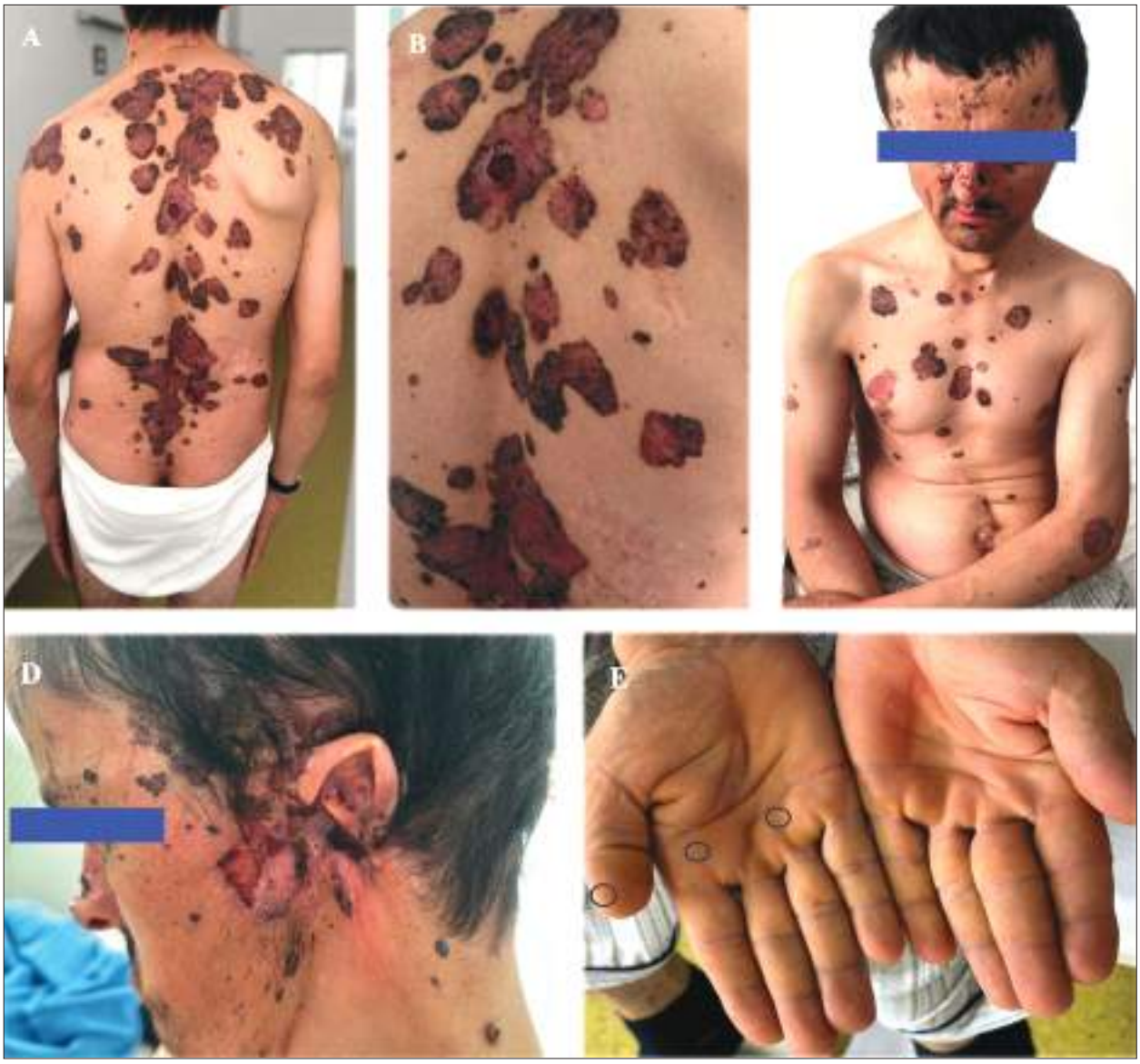

Figure 1. ***A, B****. Multiple pigmented, ulcerated tumoral lesions of variable shape and size (0.5–4 cm).* ***C.*** *Macrocephaly.* ***D.*** *Absence of the left auricular pavilion and complete obstruction of the external auditory canal (EAC).* ***E.*** *Multiple palmar depressions ("acral pits").*

("spoke-wheel structures") arising from a well-circumscribed, intensely pigmented central zone, findings typical of superficial pigmented basal cell carcinoma (Figure 4).

During hospitalization, the patient received daily local wound care with dressings applied to ulcerated areas, as well as surgical excision of a nodular pigmented lesion for histopathological examination.

Interdisciplinary consultations were also performed to ensure a comprehensive multidisciplinary assessment.

The treatment regimen included analgesics (Tramadol 50 mg, 1-0-1), vitamin therapy (Vitamin B1 100 mg/2 mL 0-1-0, Vitamin B6 250 mg/5 mL 0-1-0, Vitamin D 4000 IU 1-0-0), topical antibiotic therapy with fusidic acid cream (1-0-1),

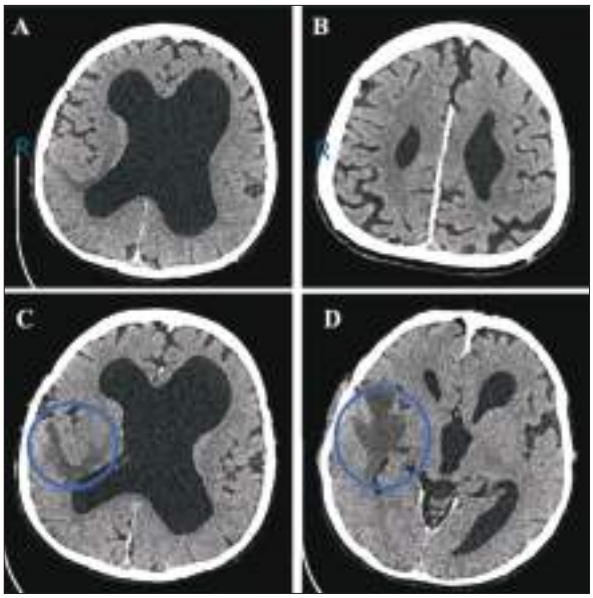

*Figure 2. **A.** Hydrocephalus. **B.** Falx cerebri calcification. **C, D.** Right anterior temporal intracranial expansive process.*

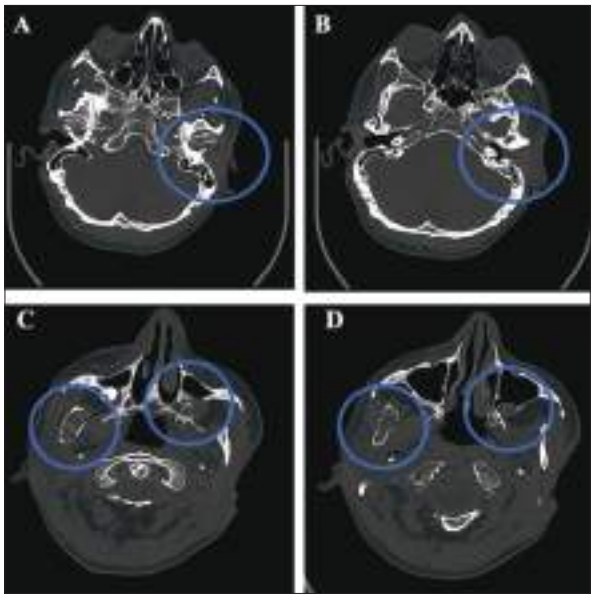

Figure 3. A, B. Left external auditory canal (EAC) obstructed by a heterogeneous tissue densification. C, D. Cystic lesions located at the level of the right mandibular ramus and the left paramedian maxilla.

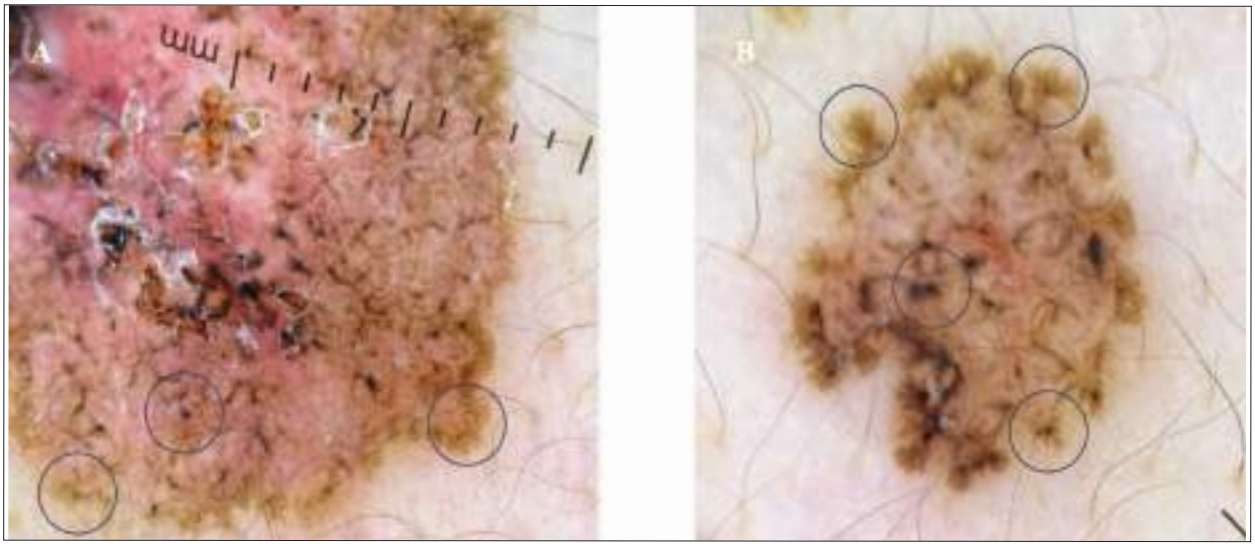

*Figure 4. **A, B.** "Maple leaf-like" structures at the periphery of the lesion and central "spoke-wheel" pattern.*

and systemic antifungal therapy with Itraconazole 100 mg (0-1-0).

Histopathological examination revealed a nodular basal cell carcinoma with a solid and reticular pattern (low-risk subtype), slightly pigmented, ulcerated, and inflamed, with a maximum diameter of 8 mm. The level of invasion was confined to the superficial dermis (Clark level III, modified Breslow index 1.5 mm), with no perineural invasion. The resection margins were reported as tumor-free, both peripherally and in depth. Immunohistochemistry showed

BerEP4 positivity, confirming the diagnosis of nodular basal cell carcinoma, staged as pT1R0 (AJCC, 8th edition).

In the presented case, the diagnosis of Gorlin-Goltz syndrome was established based on the presence of four major criteria - multiple early-onset basal cell carcinomas, radiologic evidence of falx cerebri calcification, radiographically confirmed odontogenic cysts, and palmar pits - together with three minor criteria, namely macrocephaly, skeletal abnormalities (kyphoscoliosis), and hypertelorism.

These findings fulfill the clinical diagnostic criteria according to recent guidelines, confirming the diagnosis of Gorlin-Goltz syndrome.

Discussions

Gorlin-Goltz syndrome represents a rare genetic entity with significant clinical relevance due to its potential to generate multiple basal cell carcinomas, maxillary cystic lesions, and skeletal abnormalities. The complexity of this pathology derives from the heterogeneity of its clinical manifestations, which may vary considerably even among members of the same family, often leading to delayed diagnosis or underestimation of disease severity (2).

The PTCH1 gene encodes a transmembrane receptor involved in the regulation of the Hedgehog (HH) signaling pathway, which controls cellular proliferation, differentiation, and migration. Under physiological conditions, PTCH1 inhibits the Smoothened (SMO) protein; however, inactivating mutations in PTCH1 lead to its uncontrolled activation, promoting neoplastic proliferation. Recent studies have confirmed that approximately 70–85% of patients with Gorlin syndrome harbor PTCH1 mutations, while 5–10% present SUFU mutations, which are associated with an increased risk of medulloblastoma. Aberrant activation of the Hedgehog pathway has also been linked to osteogenesis and angiogenesis, explaining the presence of intracranial calcifications and odontogenic cysts (3).

The diagnosis of Gorlin-Goltz syndrome is based on the clinical and genetic criteria updated in 2022 (4), presented in Table 1. It can be established in the presence of two major and one minor criteria, one major and three minor criteria, or through the identification of a heterozygous germline pathogenic variant in the PTCH1 or SUFU genes, confirmed by molecular genetic testing.

The differential diagnosis of Gorlin-Goltz syndrome should consider other hereditary or syndromic disorders associated with multiple basal cell carcinomas or similar cutaneous manifestations. These include Bazex-Dupré-Christol syndrome, characterized by follicular hypoplasia, skin atrophy, and basal cell carcinomas without odontogenic cysts or skeletal anomalies; Rombo syndrome, presenting with dermal atrophy, telangiectasias, and multiple BCCs in adulthood; and xeroderma pigmentosum, an autosomal recessive disorder caused by DNA repair defects, leading to severe photo-sensitivity and early-onset cutaneous malignancies (2).

Surgical treatment remains the mainstay in the management of basal cell carcinomas; however, in cases with multiple, diffuse, or recurrent lesions, this approach becomes challenging and sometimes impossible without causing severe aesthetic and functional impairment to the patient (5). In the present case, repeated excisions resulted in multiple scars and the loss of the left auricle. Such situations illustrate the limitations of surgical therapy in Gorlin-Goltz syndrome and the need for effective systemic alternatives. Over the past decade, the use of Hedgehog pathway inhibitors (Vismodegib, Sonidegib) has significantly transformed the management of advanced or inoperable basal cell carcinoma.

Table 1. Diagnostic criteria

Major criteria:
• Multiple basal cell carcinomas (≥2) or a single basal cell carcinoma occurring before the age of 20
• Histologically confirmed keratocystic odontogenic cysts
• Palmar or plantar pits
• Calcification of the falx cerebri
• First-degree relative diagnosed with Gorlin-Goltz syndrome
• Medulloblastoma diagnosed in childhood
Minor criteria:
• Macrocephaly
• Rib (bifid, fused) or vertebral anomalies
• Skeletal abnormalities (kyphoscoliosis, vertebral fusion)
• Cleft lip and/or palate
• Ocular anomalies (hypertelorism, strabismus, congenital cataract)
• Lympho-mesenteric or pleural cysts
• Ovarian or cardiac fibromas

Hedgehog pathway inhibitors act by blocking the activation of the Smoothened (SMO) protein, a key component of the signaling cascade involved in cellular proliferation and differentiation. Under physiological conditions, the PTCH1 gene inhibits SMO; however, inactivating mutations in this gene lead to uncontrolled activation of the Hedgehog pathway, stimulating the expression of target genes responsible for tumor growth (6,7). The ERIVANCE BCC study (Sekulic et al., NEJM, 2012) demonstrated an objective response rate of 43% in locally advanced cases and 30% in metastatic cases, with complete response in 21% of patients and a favorable safety profile. Nevertheless, long-term efficacy is limited by the development of secondary resistance, often caused by mutations in the SMO protein or by alternative activation of GLI transcription factors, which can reactivate the Hedgehog pathway independently of SMO (7).

Conclusions

Early diagnosis is crucial for limiting aesthetic and functional consequences, as well as for providing genetic counseling to the patient's family. The presented case illustrates a severe form of the disease, with onset during adolescence and progressive evolution over the years. The recurrent course of cutaneous lesions and the development of loco-regional complications highlight the need for continuous monitoring and multidisciplinary collaboration among the dermatologist, plastic surgeon, otolaryngologist, geneticist, and psychologist. In advanced or inoperable cases, targeted anti-Hedgehog therapies represent an effective alternative, providing significant tumor control and improving patients' quality of life. However, the development of secondary resistance and the cumulative adverse effects require caution and an individualized therapeutic approach.

The comprehensive management of patients with Gorlin-Goltz syndrome should address not only the treatment of tumor lesions but also the psychological and social dimensions of the disease, considering its profound impact on body image and emotional well-being.

In conclusion, early recognition, personalized treatment, and long-term monitoring remain essential elements for reducing morbidity and maintaining an optimal quality of life in these patients.

Bibliography

1. Richa R, Kumar V, Ayushree A. A rare case report of Gorlin-Goltz's syndrome: a multisystemic disorder of otolaryngological domain. Egyptian Journal of Otolaryngology. 2023 Dec 1;39(1).
2. Bresler SC, Padwa BL, Granter SR. Nevoid Basal Cell Carcinoma Syndrome (Gorlin Syndrome). Head Neck Pathol. 2016 Jun 1;10(2):119–24.
3. Feng Z, Zhu S, Li W, Yao M, Song H, Wang RB. Current approaches and strategies to identify Hedgehog signaling pathway inhibitors for cancer therapy. Vol. 244, European Journal of Medicinal Chemistry. Elsevier Masson s.r.l.; 2022.
4. Nosé V, Lazar AJ. Update from the 5th Edition of the World Health Organization Classification of Head and Neck Tumors: Familial Tumor Syndromes. Head Neck Pathol. 2022 Mar 1;16(1):143–57.
5. Basset-Seguin N, Herms F. Update on the management of basal cell carcinoma. Vol. 100, Acta Dermato-Venereologica. Medical Journals/Acta D-V; 2020. p. 284–90.
6. Sekulic A, Migden MR, Oro AE, Dirix L, Lewis KD, Hainsworth JD, et al. Efficacy and Safety of Vismodegib in Advanced Basal-Cell Carcinoma. New England Journal of Medicine. 2012 Jun 7;366(23):2171–9.
7. Feng Z, Zhu S, Li W, Yao M, Song H, Wang RB. Current approaches and strategies to identify Hedgehog signaling pathway inhibitors for cancer therapy. Vol. 244, European Journal of Medicinal Chemistry. Elsevier Masson s.r.l.; 2022.

Conflict de interese
NEDECLARATE

Conflict of interest
NONE DECLARED

Correspondance address: Daniela-Vasilica Șerban
Municipal Emergency Clinical Hospital, Department of Dermatology and Venereology, Timișoara
E-mail: daniela.serban@umft.ro