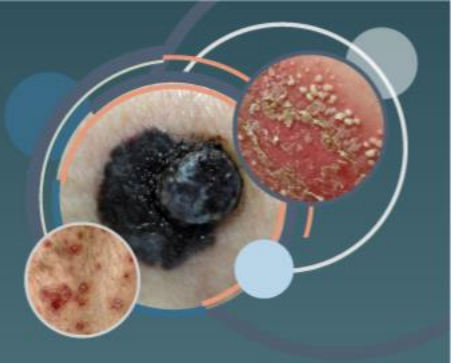
SCUOLA DERMATOLOGICA
SERGIO CHIMENTI

ROMA 17-18 Maggio 2024
Roma Eventi - Piazza di Spagna - Via Alibert 5A, 00187 Roma

1° INCONTRO 2024 YES or NO CONTEST

Dermatology Update



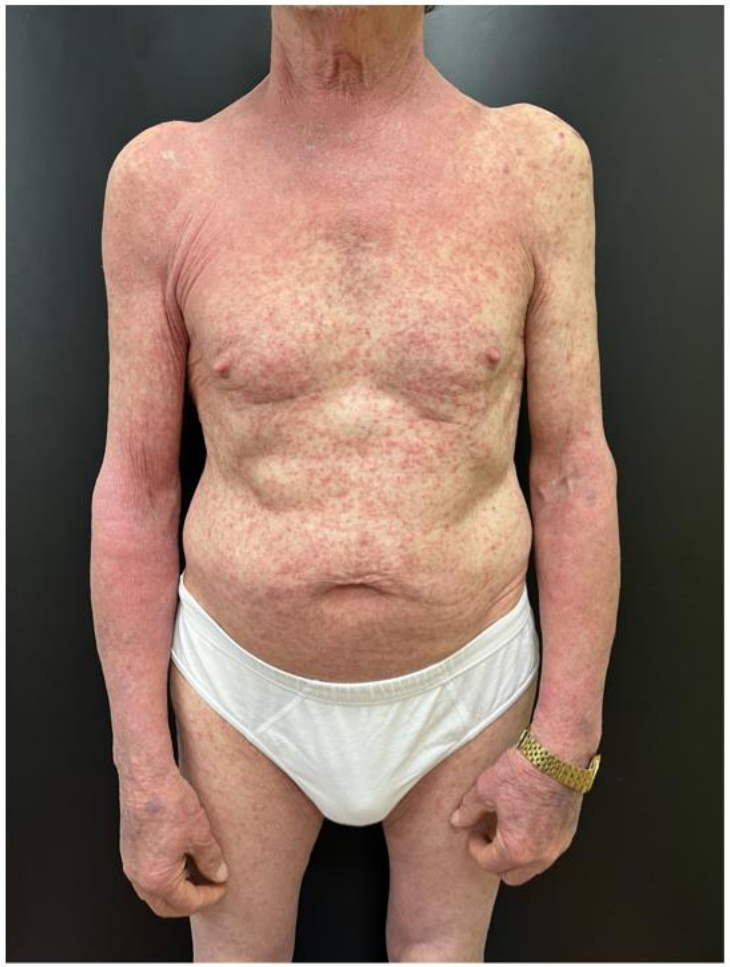
Alessandro Giunta

Fondazione PTV Policlinico Tor Vergata

Sessione Match "Yes or No" - La dermatologia in consulenza

Casistica clinica

Clinical case: consultation from the Nephrology Unit



74 years old man referred for generalized papular eruption at chest from the Nephrology Unit 2 SUD. The patient was admitted to hospital for a nephrotic syndrome with hypereosinophilia arose during treatment with ustekinumab for UC

Renal biopsy: focal segmental glomerulosclerosis (FSGS); Congo Red - and Ig4 -

Parameter	Value	Referral values
Red blood cells	3,26 milion/µL	4,40-6,00
Hb	10,30 g/dL	13,00-18,00
Hematocrit	29,80%	36,00-51,00
Azotaemia	61,0 mg/dl	18,00-55,00
Uricemia	2,80 mg/dl	3,50-7,20
Calcium	7,40 mg/dl	8,80-10,00
Inorganic phosphate	1,80 mg/dl	2,30-4,70
Albumin	1,80 gr/dl	3,20-4,60
Microalbuminuria (24h)	4621,50 mg/24h	0,00-30,00
Urine Creatinine (24h)	820,80 mg/24h	870,00-2410,00
Urine Proteins (24h)	6570,00 mg/24h	≤300,00
Creatinine clearance	56,44 ml/min	61,00-147,00

1. A. Giunta. Personal experience, for educational purpose only

1. La FSGS è un effetto collaterale grave di ustekinumab?

1. SI
2. NO

PER RISPONDERE collegati con il tuo smartphone a: meeter.it/yon

FGSC and Ustekinumab: review of **published evidences**

100 NEFROLOGIA. 2019;39(1):84–109

Nephrotic syndrome in relation to treatment with ustekinumab☆

Síndrome nefrótico en relación con tratamiento con ustekinumab

Dear Editor,

In recent years, monoclonal antibody therapy has increased exponentially, acquiring particular importance in patients with autoimmune diseases who are refractory to standard therapy. The use of these biological drugs has delivered great hope to this group of patients, as they have demonstrated promising results. The main drawback of these drugs is the current lack of knowledge on their possible side effects, due mainly to the fact that their use only started very recently and, therefore, experience with them in both the short- and long-term is limited.

An example of use of these treatments in the field of Dermatology is in psoriasis,[1] where the most commonly used drugs are adalimumab (Humira®) and ustekinumab (Stelara®).[2–4] The latter is an IgG1 kappa antibody, which acts through specific binding to the p40 subunit of interleukins 12 and 23, thereby preventing the interaction of these interleukins with their receptor. Through this mechanism, it is possible to block the activation pathway of natural killer cells and T cells, as well as to prevent the differentiation of CD4+ T cells from Th1 cells (helper cells).[5,6]

After reviewing the literature, we did not find any relationship between this treatment and nephrotic syndrome. We therefore consider this review interesting.

We present the case of a 51-year-old male with dyslipidaemia, undergoing treatment with statins and with a history of renal lithiasis of the left kidney during his youth, and undergoing follow-up by Dermatology for plaque psoriasis predominantly affecting the upper limbs, trunk and scalp. He had received treatment with Neotigason® (acitretin), topical corticosteroids, vitamin D analogues and ultraviolet A radiation, presenting a good response to treatment, but with re-occurrence of the lesions after its withdrawal. In this context, therapy was started with adalimumab, resulting in a partial response. In view of the persistent scalp and trunk lesions, it was decided to change to ustekinumab. This drug was administered in accordance with the normal induction regimen of 45 mg, followed by another 45 mg after four weeks, subsequently administering the next doses every 12 weeks.[7] Approximately two years after starting treatment, when he had received a total dose of 585 mg, a few days after administration of the last dose, the presence of proteinuria was observed in the sitematic urinary analysis that was confirmed in a 24-h urine sample. Initially the proteinuria was 3.7 g/day and it was accompanied by mild hypoalbuminemia (albumin 3.2 g/dl) with increased levels of cholesterol and triglycerides, maintaining preserved kidney function. He was therefore referred to Nephrology to test for possible glomerulopathy.

During one of our visits, the patient mentioned foamy urine, which he had been experiencing for a few weeks, without observing haematuria or other symptoms. Considering the possibility of glomerulonephritis it was tested for immunoglobulins, complement, with blood and urine electrophoresis, ANA, ANCA and viral serology. The results confirmed the presence of nephrotic syndrome. The remaining complementary tests were normal or negative. Finally, in view of the findings obtained, an ultrasound-guided percutaneous kidney biopsy was performed.

A total of 19 glomeruli were observed in the pathological study, none of which were completely sclerosed. The vast majority presented frequent synechiae between the tuft and Bowman's capsule. Discrete segmental consolidations were identified in three glomeruli. Focal segmental granular deposits of IgM and C3 were identified on the direct immunofluorescence study. Due to the above, he was diagnosed of focal segmental glomerulosclerosis classic type variant (Fig. 1).

Given the temporal relationship between the administration of the treatment and the onset of proteinuria, it was decided to discontinue ustekinumab in light of suspected side effects from treatment. Concomitant treatment with prednisone was also started at the standard treatment dose in accordance with the KDIGO guidelines used for the management of symptoms of primary glomerulosclerosis (mg/kg of weight).[8] In this case, it was not possible to combine renin–angiotensin–aldosterone system inhibitors due to the patient's symptomatic hypotension. In the following visits, he presented favourable progress, testing negative for proteinuria and recovering from hypoalbuminemia from the first month of treatment initiation and discontinuation of ustekinumab. This rapid response, along with the absence of hypertension and microhaematuria, point to the diagnosis of side effects to treatment in the face of primary-origin glomerulonephritis. Despite this, it was decided to complete 12 weeks of oral prednisone, with progressive withdrawal until discontinuation. Currently, the patient continues to show no signs of active kidney disease (absence of proteinuria and normal kidney function) (Fig. 2).

DOI of original article:
https://doi.org/10.1016/j.nefro.2018.06.003.

☆ Please cite this article as: Fernández MP, Piteiro Bermejo AB, Peña Esparragoza JK, Martínez AB, Moreno IA, Ramos JM, et al. Síndrome nefrótico en relación con tratamiento con ustekinumab. Nefrologia. 2019;39:100–102.

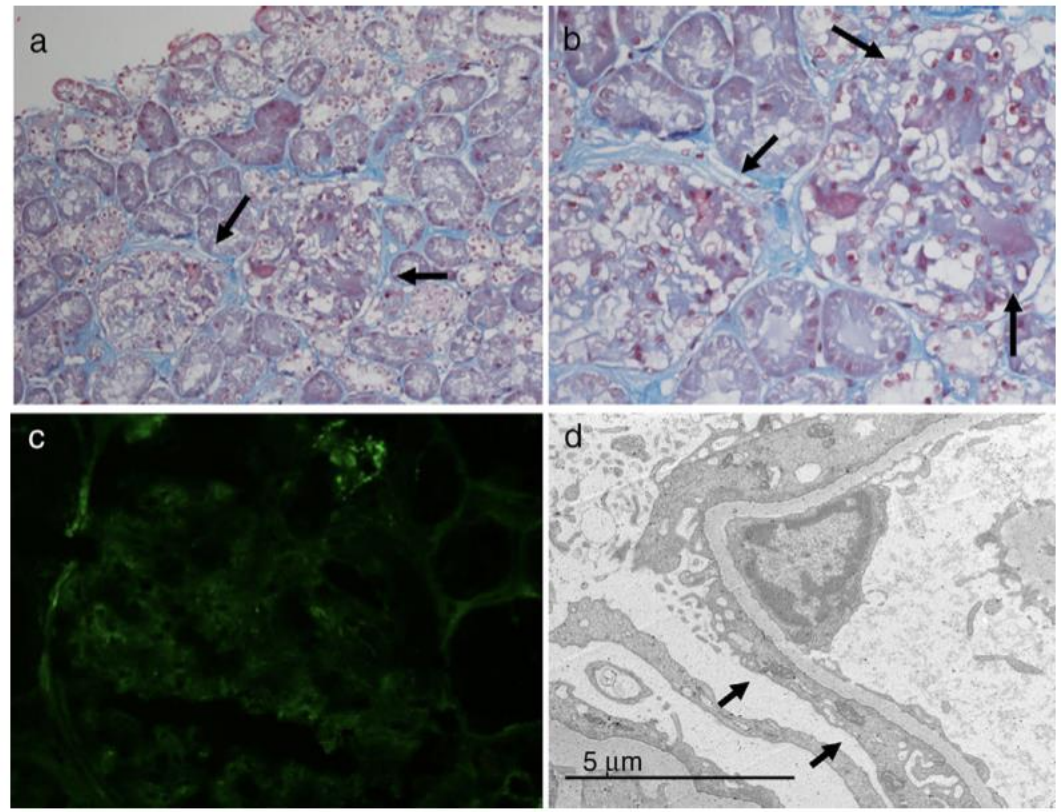
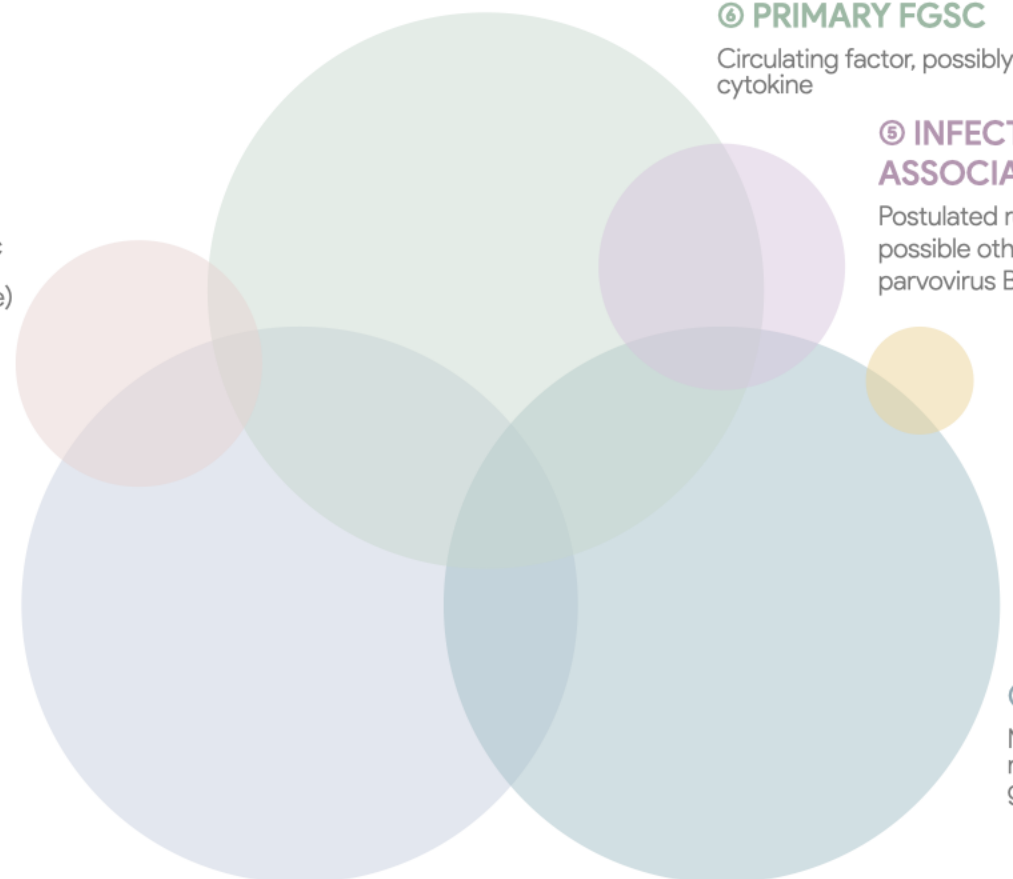


Figure 1. Kidney biopsy. (a and b) Optical microscopy: areas of mesangial collapse and focal segmental glomerulosclerosis. (c) Immunofluorescence: C3 deposits. (d) Electron microscopy: diffuse effacement of podocyte processes.

1. Pérez Fernández M, et al. Nephrotic syndrome in relation to treatment with ustekinumab. Nefrologia (Engl Ed). 2019;39:100-102

FGSC: review of **published evidences**



⑥ PRIMARY FGSC

Circulating factor, possibly a cytokine

⑤ INFECTION/INFLAMMATION ASSOCIATED FGSC

Postulated role of IFN and possible other cytokines (HIV, CMV, possible: parvovirus B19, Still disease, natural killer cell leukemia)

① GENETIC FGSC

High-penetrance genetic variants (Mendelian or mitochondrial inheritance)

④ MEDICATION/TOXINE ASSOCIATED FGSC

Presumed direct effect on podocytes

② APOL1 FGSC

APOL1 variant-initiated inflammation

③ ADAPTATIVE FGSC

Mismatch between metabolic load and glomerular capacity

1. Rosenberg AZ, Kopp JB. Focal Segmental Glomerulosclerosis. Clin J Am Soc Nephrol. 2017;12:502-517

IBDs and FGSC: review of **published evidences**

Inflammatory Bowel Diseases, 2023, **29**, 1306–1316
https://doi.org/10.1093/ibd/izac140
Advance access publication 9 August 2022
Review Article - Clinical

Renal and Urological Disorders Associated With Inflammatory Bowel Disease

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Renal and urinary tract complications related to inflammatory bowel disease (IBD) have been relatively understudied in the literature compared with other extraintestinal manifestations. Presentation of these renal manifestations can be subtle, and their detection is complicated by a lack of clarity regarding the optimal screening and routine monitoring of renal function in IBD patients. Urolithiasis is the most common manifestation. Penetrating Crohn's disease involving the genitourinary system as an extraintestinal complication is rare but associated with considerable morbidity. Some biologic agents used to treat IBD have been implicated in progressive renal impairment, although differentiating between drug-related side effects and deteriorating kidney function due to extraintestinal manifestations can be challenging. The most common findings on renal biopsy of IBD patients with renal injury are tubulointerstitial nephritis and IgA nephropathy, the former also being associated with drug-induced nephrotoxicity related to IBD medication. Amyloidosis, albeit rare, must be diagnosed early to reduce the chance of progression to renal failure. In this review, we evaluate the key literature relating to renal and urological involvement in IBD and emphasize the high index of suspicion required for the prompt diagnosis and treatment of these manifestations and complications, considering the potential severity and implications of acute or chronic loss of renal function. We also provide suggestions for future research priorities.

Lay Summary

Renal and urinary tract complications related to inflammatory bowel disease (IBD) are important but have been neglected in the literature. We emphasize the high index of suspicion required for the prompt diagnosis, treatment, and prevention of these manifestations and complications.

Key Words: inflammatory bowel disease, Crohn's disease, ulcerative colitis, renal disease, extraintestinal manifestation

Introduction

Besides the gastrointestinal tract, inflammatory bowel disease (IBD) can also manifest in extraintestinal organs, contributing significantly to morbidity and mortality.[1,2] These extraintestinal symptoms of IBD are divided into extraintestinal complications and extraintestinal manifestations (EIMs). Extraintestinal complications refer to manifestations that are direct or indirect sequelae of intestinal inflammation.[1] In contradistinction, EIMs have been defined as "an inflammatory pathology in a patient with IBD that is located outside the gut and for which the pathogenesis is either dependent on extension/translocation of immune responses from the intestine, or is an independent inflammatory event perpetuated by IBD or that shares a common environmental or genetic predisposition with IBD."[3] They likely represent a composite of systemic inflammation, autoimmune susceptibility, and metabolic and nutritional derangement. Extraintestinal manifestations are due to an inflammatory process occurring outside the gut but are related to the underlying diagnosis of IBD; their clinical spectrum varies from mild, transient disease to severe, disabling complications. The reported frequencies of EIMs in IBD range from 6% to 47%; the heterogeneity in reported prevalence is likely due to the variability in definitions used for EIMs and because patients can be affected by multiple EIMs.[1] Almost any organ can be affected, but involvement of the joints, skin, eyes, liver, and biliary tract are the most commonly described EIMs.[3] Renal complications in IBD (Table 1) have received much less attention despite early studies reporting kidney involvement in nearly 25% of IBD patients.[4,5] In these early reports, nephrolithiasis, obstructive uropathy, and fistula formation between the bowel and urinary tract were the most common occurrences.

Renal parenchymal involvement in IBD has also been described in the form of glomerulonephritis, tubulointerstitial nephritis, and amyloidosis. However, its true prevalence is not clear because systematic analyses are lacking.[6] In recent years, the use of more potent drugs for treating IBD has increased the potential for nephrotoxicity, further highlighting the importance of this topic.[7] Parenchymal renal involvement can affect any or all of the glomerular, tubular, or interstitial compartments. It is the purpose of this review to report and evaluate the key data in the literature on renal involvement in IBD. We emphasize the high index of suspicion required for the prompt diagnosis, treatment, and ideally prevention of these manifestations and complications; we also highlight some practical considerations in clinical practice.

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Table 1. Renal and urological disorders associated with inflammatory bowel disease.

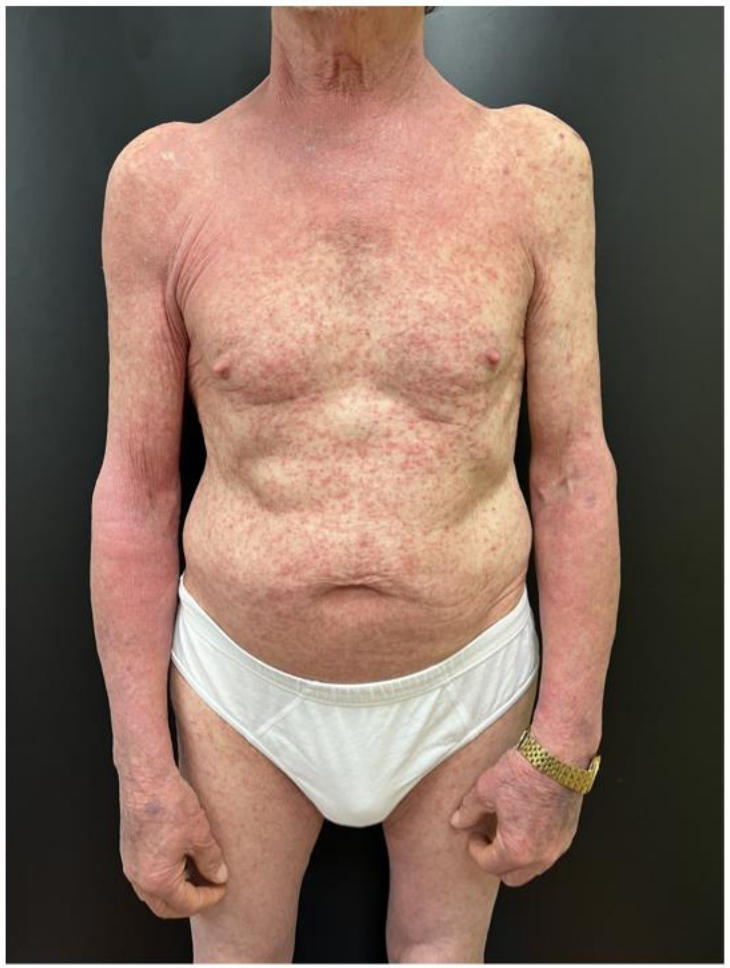
Nephrolithiasis
Calcium oxalate
Uric acid
Entero-vesical fistulae
Urinary tract malignancy
Kidney cancer
Urethral cancer
Bladder cancer
Drug-related nephrotoxicity
Glomerulonephritis
IgA nephropathy
Minimal change disease
IgM nephropathy
Membranous nephropathy
Membranoproliferative nephropathy
Focal and segmental glomerulosclerosis
Antiglomerular basement disease
Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)
Tubulointerstitial disease
Acute tubular injury
Tubulointerstitial nephritis
Renal amyloidosis

The reported frequencies of EIMs in IBD range from 6% to 47%; the heterogeneity in reported prevalence is likely due to the variability in definitions used for EIMs and because patients can be affected by multiple EIMs

Renal complications in IBD have received much less attention despite early studies reporting kidney involvement in nearly 25% of IBD patients

1. Kumar S, et al. Renal and Urological Disorders Associated With Inflammatory Bowel Disease. Inflamm Bowel Dis. 2023;29:1306-1316

Clinical case: consultation from the Nephrology Unit



Università degli Studi di Roma "Tor Vergata"
Azienda Ospedaliera Universitaria Policlinico Tor Vergata
U.O.S.D. Anatomia Patologica ad Indirizzo Istopatologico
Responsabile di anatomia patologica Prof. Augusto Orlandi
UOSD di Anatomia patologica ad indirizzo citopatologico
Responsabile Prof. Alessandro Mauriello

REGIONE LAZIO

Esame n° **I / 2023 / 15905** del 22/11/2023

[redacted] Età: 74

Medico richiedente : DR.GIUNTA
Ente : **POLICLINICO TOR VERGATA**
Provenienza : U.O.C. DERMATOLOGIA - AMBULATORIALE INTERNO

MATERIALE INVIATO:
Neoformazione cutanea regione deltoidea dx

MACROSCOPIA:
Losanga di cute di cm 1x0,4 sede di du macule pigmentate periferiche ed opposte di cm 0,1 ciascuna. Prelievi: un cestello in toto.

Dott. Alberto Broglio

MICROSCOPIA:
Cute sede di pustola intracornea con polimorfonucleati neutrofili e necrosi epidermica fino al derma superficiale. Il derma superficiale mostra modesta flogosi cronica perivascolare con sparsi neutrofili.

DIAGNOSI:
Reperti morfologici compatibili con una dermatite neutrofilica.

DATA REFERTO:
04/12/2023

Patologo
Prof. Amedeo Ferlosio

Specializzando
Dott. Gabriele Rotondaro

Specializzando
Dott.ssa Lucrezia Bertini

Specializzanda
Dott.ssa Fausta Di Loreto

TOR VERGATA

Rappresentazione di un referto firmato elettronicamente, secondo la normativa vigente
Nome Certificato ITALMDATOL30H501C Firmatario: Prof. Amedeo Ferlosio
Data e ora della firma: 04/12/2023 12:28:59 - Id Referto: I2023159905
Il referto è conservato secondo la normativa in vigore.

Viale Oxford, 81 - 00133 Roma
Centralino 06 33 901 - Fax 06.20.90.02.10
e-mail: poliambu.torvergata@ptvonline.it

1. A. Giunta. Personal experience, for educational purpose only

Neutrophils and inflammation

A critical role of inflammation is to deliver neutrophils and other leukocytes to a site of injury and to activate these cells to perform their function of protecting the host against infection

Neutrophils are among the first cells to arrive at sites of inflammation; reasons for this include their abundance in the bloodstream and their rapid response to chemokines. When activated, neutrophils move at speeds up to 30 µm/min – the fastest cell in the body

The motile responses of neutrophils to microbial infection include emigration out of the vasculature and movement toward the source of the inflammatory chemoattractant. This culminates in the phagocytic ingestion of opsonized microbes

The price to be paid for the defensive potency of neutrophils for destroying microbes and necrotic tissues is that they can injure normal tissue. During activation and phagocytosis, neutrophils release products (e.g. lysosomal enzymes, reactive oxygen intermediates, products of arachidonic acid metabolism [prostaglandins and leukotrienes]) not just within the phagolysosome, but also into the extracellular space. Endothelial injury and tissue damage ensue, thus contributing to a number of acute and chronic diseases that affect the skin as well as other organs

1. Jorizzo JL, et al. Neutrophilic vascular reactions. J Am Acad Dermatol 1988;19:983-1005

Neutrophils and inflammation: **neutrophilic dermatoses**

The neutrophilic dermatoses constitute a heterogeneous but linked spectrum of diseases, with significant overlapping histopathologic findings and similar pathogenic mechanisms and therapeutic approaches

They are often associated with underlying internal diseases, which may have significant morbidity and mortality. Histologically, these disorders are characterized by perivascular and diffuse neutrophilic infiltrates without any identifiable infectious agents

The cutaneous manifestations vary from vesciculo-pustules and plaques to nodules and ulcers. It is noteworthy that there may be several different types of lesions in the same patient. The dermatosis may be localized or more widespread, and, in an occasional patient, similar sterile neutrophilic infiltrates may be seen in the eyes, joints, bones, lung, liver and lymph nodes

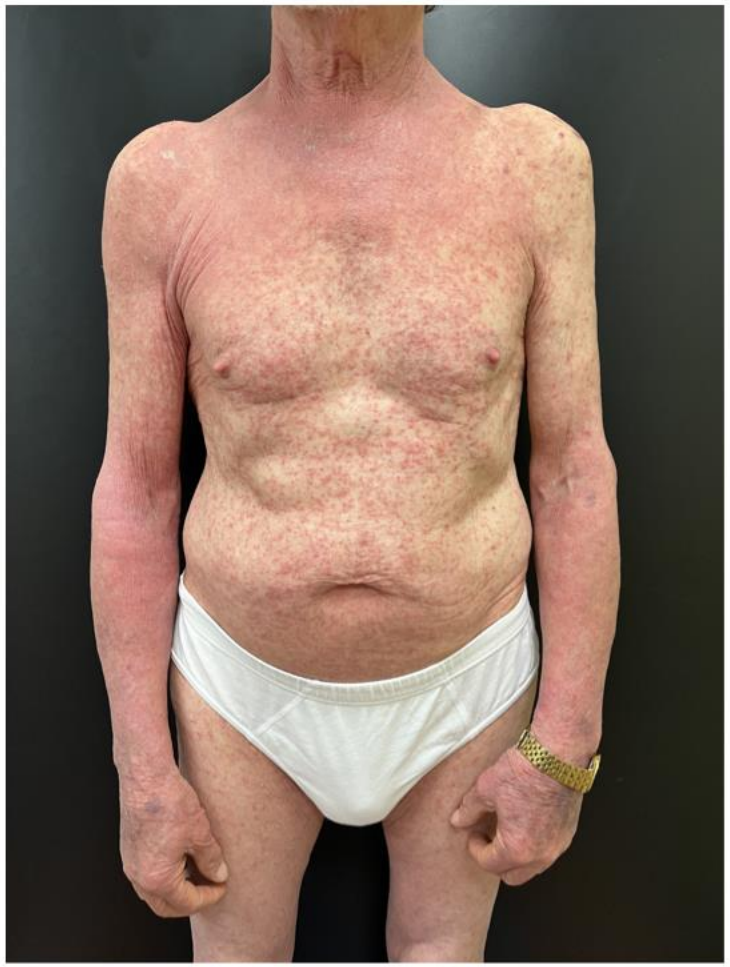
1. Jorizzo JL, et al. Neutrophilic vascular reactions. J Am Acad Dermatol 1988;19:983-1005

Neutrophilic dermatoses (non infectious)

Epidermal	Primary dermal			
	w/ vasculitis		*w/ or w/o vasculitis*	*w/o vasculitis*
A. Pustular psoriasis	A. Sweet's syndrome [a]	Bullous dermatoses	Neutophilic dermatosis (pustular vasculitis) of the dorsal hands	A. Small vessels vasculitis (leujocytoclastic vasculitis)
B. Drug induced/acute generalized exanthematous pustolosisi	B. Pyoderma *gangrenousum*	a. Dermatitis herpetiformis		*B.* Erythema *elavatum dutinum*
C. Keratoderma blennorrhagicum	C. Bechet disease [b]	b. Linear IgA bullous dermatosis		C. Medium vessels vasculitis
D. Sneddon-Wilkinson disease	D. Bowel associated dermatosis-arthritis syndrome	c. Bullous systemic lupus erythematosus		
E. IgA pemphigus	E. Inflammatory bowel disease [b]	d. Inflammatory epidermolysis bulls acquisita		
a. Subcorneal pustular dermatosis type	F. Neutrophilic eccrine hidradenits			
b. Intraepidermal neutrophilic IgA dermatosis type	G. Rheumatoid neutrophilic dermatitis			
F. Amicrobialpustolosis of the folds	H. Neutrophilic urticaria			
G. Infantile acropustolosis	I. Sill's disease			
H. Tansient neonatal pustolosis	J. Erythema *marginatum*			
	K. Peeriodic fever syndrome			

(a) minority of patients have evidences of small vasculitis changes (b) patients may have small vessels vasculitis

Clinical case: IBD multidisciplinary meeting



1. A. Giunta. Personal experience, for educational purpose only

2. Non è possibile utilizzare risankizumab in un paziente con RCU e non morbo di Crohn

1. SI
2. NO

Risankizumab and Ulcerative Colitis

Risankizumab Induction Therapy in Patients With Moderately to Severely Active Ulcerative Colitis: Efficacy and Safety in the Randomized Phase 3 INSPIRE Study

Risankizumab is a humanized monoclonal antibody that binds to the IL-23 p19 subunit, inhibiting IL-23–mediated signaling and the related inflammatory cytokine cascade.[1] The INSPIRE study, a phase 3, double-blind, placebo-controlled trial, was designed to evaluate the efficacy and safety of risankizumab as induction therapy in patients with moderately to severely active UC. In a presentation by Loftus and colleagues, the primary efficacy and safety results at week 12 from the INSPIRE study were reported.[2]

Patients enrolled in INSPIRE had an intolerance or inadequate response to conventional and/or advanced therapies for UC. No prior exposure to ustekinumab or IL-23 inhibitors was permitted. A total of 975 patients comprised the intention-to-treat population; patients were randomized in a 2:1 fashion to either placebo or 1200 mg risankizumab IV administered at weeks 0, 4, 8, and 12. Following induction therapy, responding patients were eligible for enrollment in the COMMAND maintenance study, whereas nonresponding patients were eligible for an additional 12 weeks of induction treatment.

The primary endpoint of clinical remission at week 12 was significantly higher with risankizumab vs placebo (20.3% vs 6.2%; 95% CI, 10.0-18.0; *P*<.00001) (Figure 5). A benefit with risankizumab compared with placebo was observed in patients with an inadequate response to prior nonadvanced therapy (29.7% vs 8.4%) as well as in patients with an inadequate response to prior advanced therapy (11.4% vs 4.3%). The secondary endpoints of clinical response were also significantly improved with risankizumab vs placebo both at week 4 (52.2% vs 30.5%; 95% CI, 15.6-28.1; *P*<.00001) and week 12 (64.3% vs 35.7%; 95% CI, 22.3-34.8; *P*<.00001).

Several measures of endoscopic and histologic improvements at week 12 were also significantly improved with risankizumab compared with placebo. These included endoscopic improvement (36.5% vs 12.1%; 95% CI, 19.3-29.4; *P*<.00001), endoscopic remission (10.6% vs 3.4%; 95% CI, 4.2-10.2; *P*<.00001), HEMI (24.5% vs 7.7%; 95% CI, 12.3-21.0; *P*<.00001), and histologic-endoscopic mucosal remission (HEMR; 6.3% vs 0.6%; 95% CI, 3.5-7.7; *P*<.00001). Risankizumab was associated with improvements in a number of patient-reported outcomes, such as no bowel urgency (44.1% vs 27.7%; 95% CI, 10.3-22.4; *P*<.00001), no nocturnal bowel movements (67.3% vs 43.1%; 95% CI, 17.9-30.5; *P*<.00001), and no abdominal pain (35.8% vs 26.5%; 95% CI, 3.4-15.3; *P*<.00001).

Reported safety results were consistent with the already known toxicity profile of risankizumab across other indications. The 3 most common adverse events (reported by ≥5% in either treatment arm) were COVID-19 infection (4.8% with risankizumab vs 5.9% with placebo), anemia (3.4% vs 6.5%), and worsening of UC (1.7% vs 10.2%). There were no adjudicated cases of major cardiovascular event,

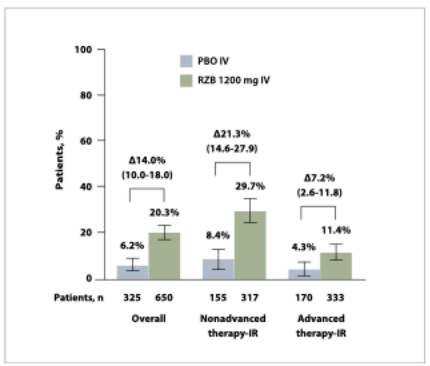


Figure 5. Clinical remission[a] at week 12 of RZB induction therapy in patients with moderately to severely active ulcerative colitis from the phase 3 INSPIRE study.

[a]Clinical remission per Adapted Mayo score: SFS ≤1 and not greater than baseline, RBS of 0, and endoscopic subscores ≤1 without friability. Results reported as adjusted treatment difference RZB vs PBO, % (95 CI) and are based on nonresponder imputation incorporating multiple imputations (NRI-MI) to handle missing data owing to COVID-19 or owing to geopolitical conflict in Ukraine or surrounding areas.

IR, inadequate response; IV, intravenous; PBO, placebo; RBS, rectal bleeding subscore; RZB, risankizumab; SFS, stool frequency subscore.

Adapted from Loftus et al. Abstract 35. Presented at: ACG 2023; October 20-25, 2023; Vancouver, Canada.[2]

Inflammatory Bowel Diseases, 2022, **28**, e140–e141
https://doi.org/10.1093/ibd/izac072
Advance access publication 13 April 2022
Letter to the Editor

CROHN'S & COLITIS FOUNDATION

Letter to the Editor

Patient With Ulcerative Colitis and Failure of Ustekinumab Responds to Risankizumab: Similar Is Not Identical

Yonatan Ziv, MD,*,[O] Arun Swaminath, MD,†,[O] and Keith Sultan, MD‡

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To the Editors,

Currently, targeted biologics for ulcerative colitis (UC) include the anti-TNF-α medications infliximab, adalimumab, golimumab, the anti-integrin vedolizumab, and ustekinumab, targeting the p40 subunits of both interleukin (IL)-12 and IL-23. New small molecule therapies include the JAK inhibitor tofacitinib and the SIP receptor modulator ozanimod.

Recent guidelines on the management of nonimmune biologic failure suggest switching to a therapy with an entirely different mechanism of action.[1,2] Notably, the next wave of therapies includes drugs with mechanisms either overlapping or similar to those already available. It is currently unclear whether these newer drugs might be effective rescue therapy following failure of their similar "cousin" medications.

Risankizumab, a selective inhibitor to the p40 subunit of IL-23 is currently approved for the treatment of psoriasis and psoriatic arthritis. Phase 3 clinical trials of risankizumab for UC are in progress.[3] It is unknown whether patients with a failure of ustekinumab might respond to risankizumab.

We present a 70-year-old male diagnosed with left-sided colitis at 66 years of age. Medical history includes deep venous thrombosis (DVT) on apixaban and mild/inactive psoriasis. He reports loose, bloody stools 10 times daily. Following failure of prednisone and mesalamine, he began vedolizumab from August 2017 through February 2019, eventually as frequently as every 4 weeks. This was followed by failure of ustekinumab from April 2019 to February 2020, also accelerated to every 4-week dosing, confirmed by colonoscopy demonstrating Mayo 3 score (Figure 1A). The patient then tied infliximab through November 2020, experiencing nonimmune failure and trough level 9.1 ug/mL. The patient requested a second course of vedolizumab, which was given from November 2020 to March 2021 without any clinical or endoscopic response. Given his DVT history, the patient declined tofacitinib, and ozanimod was not yet approved for UC. He was subsequently started receiving 150 mg of risankizumab subcutaneously at weeks 0, 4, and then every 12 weeks. The patient rapidly reported decreased urgency and

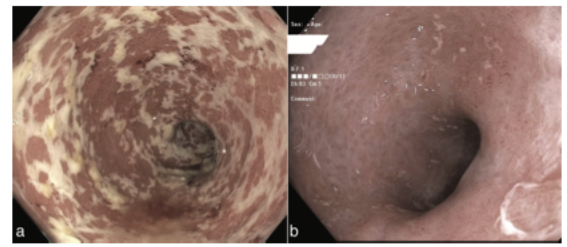
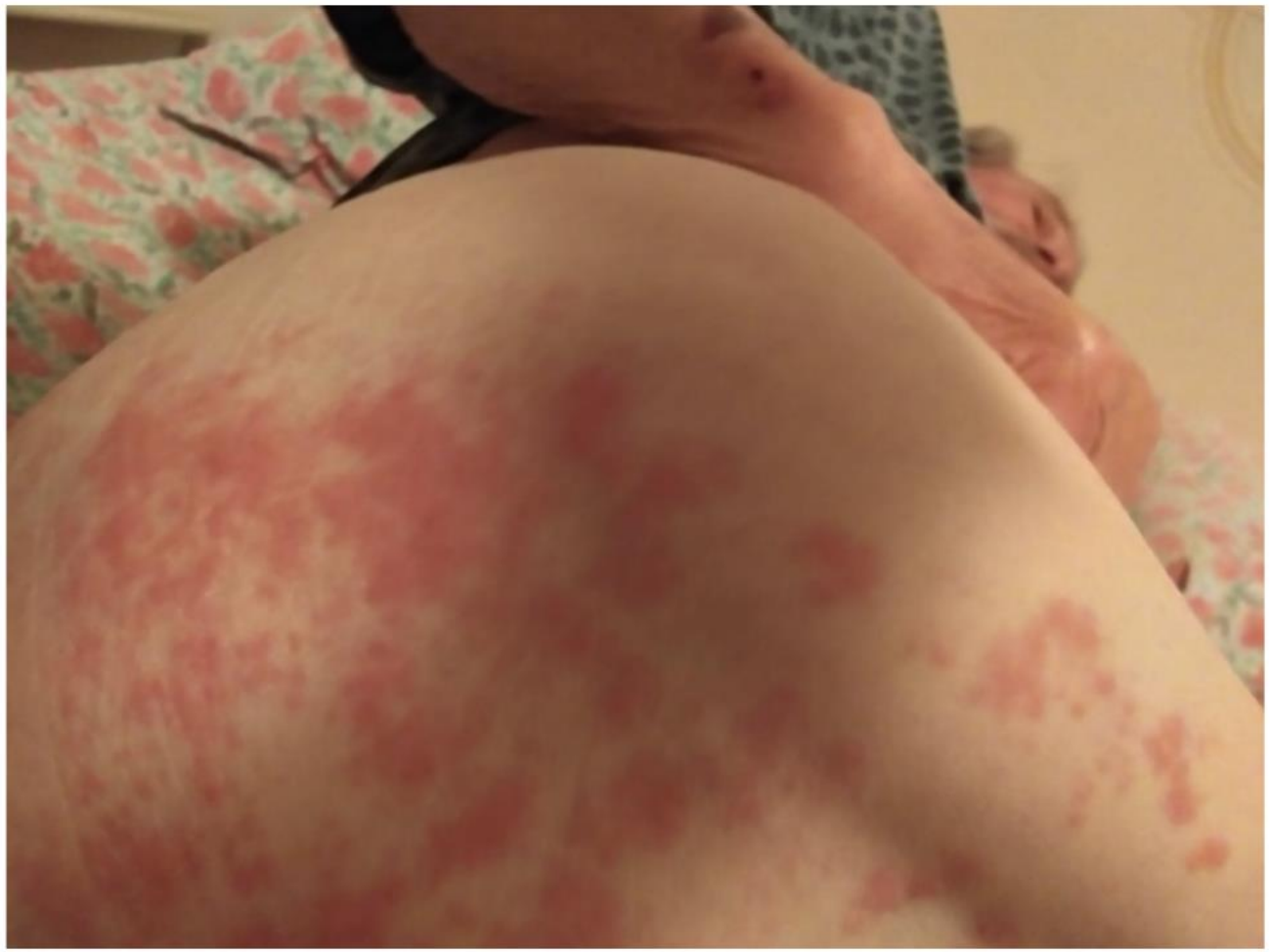


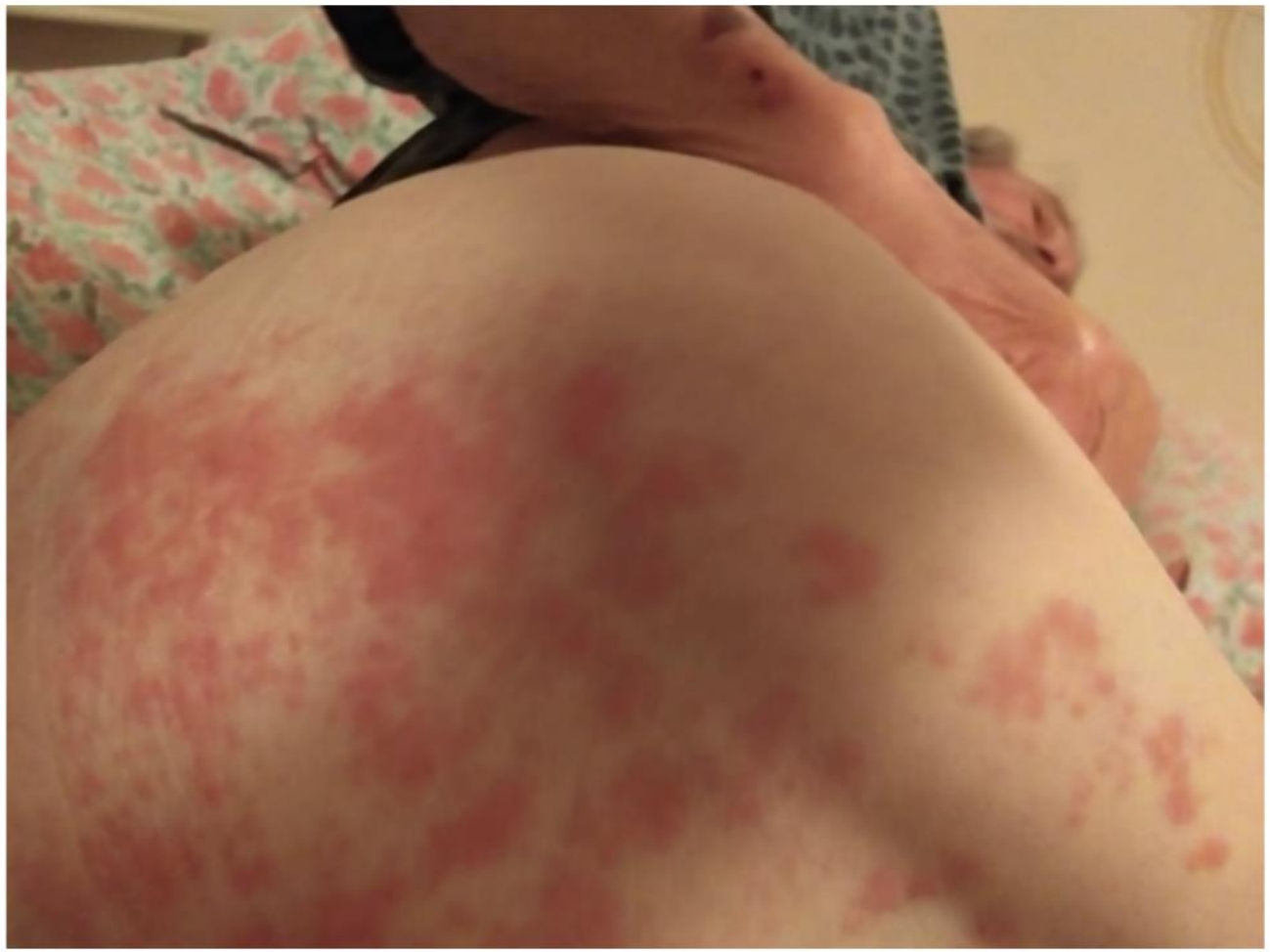
Figure 1. A, Sigmoid colon following ustekinumab. B, Sigmoid colon following risankizumab.

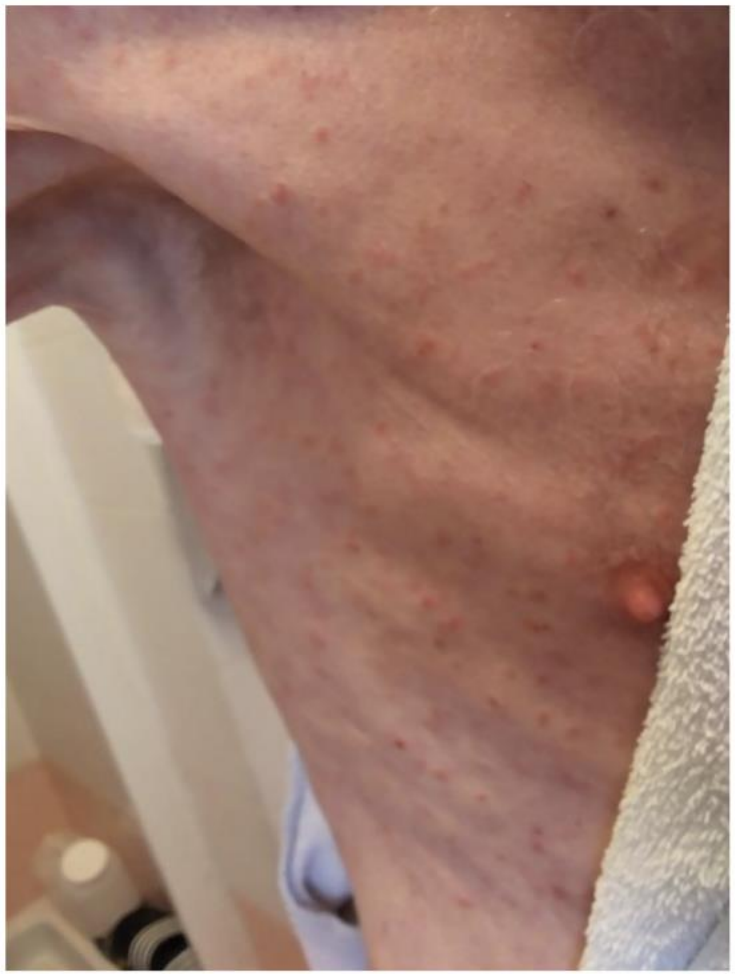
Clinical case: Whatsapp consultation (sic!)



1. A. Giunta. Personal experience, for educational purpose only

Clinical case: Whatsapp consultation (sic!)



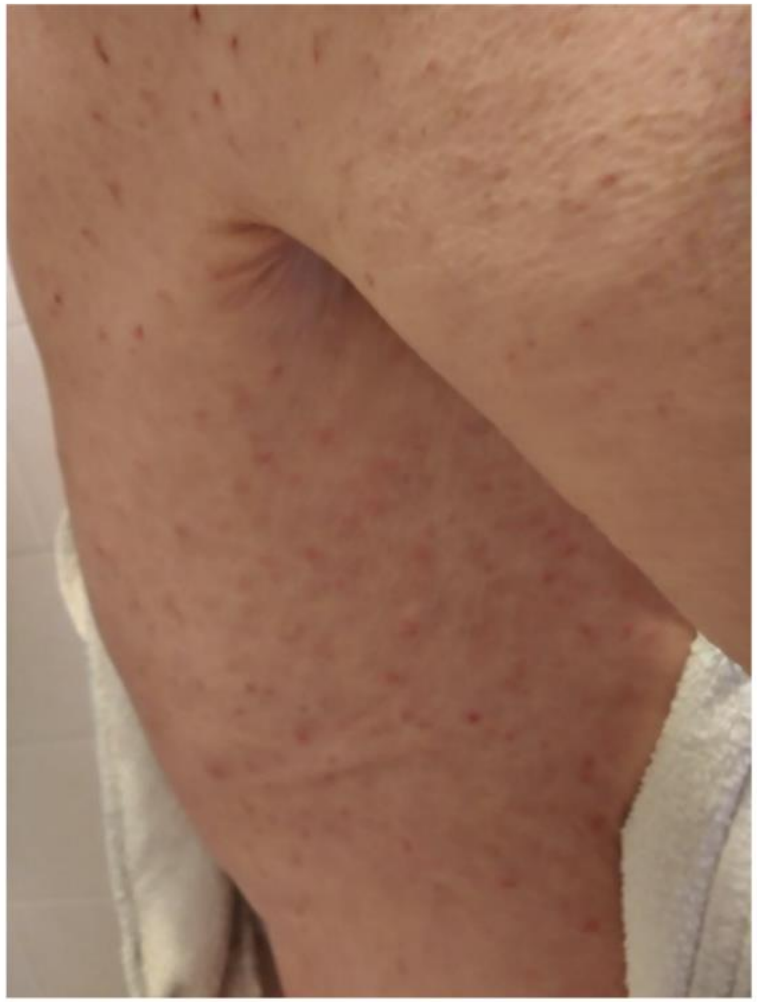


1. A. Giunta. Personal experience, for educational purpose only

1. Le lesioni sono compatibili con una inefficacia secondaria e il trattamento deve essere modificato

1. SI
2. NO

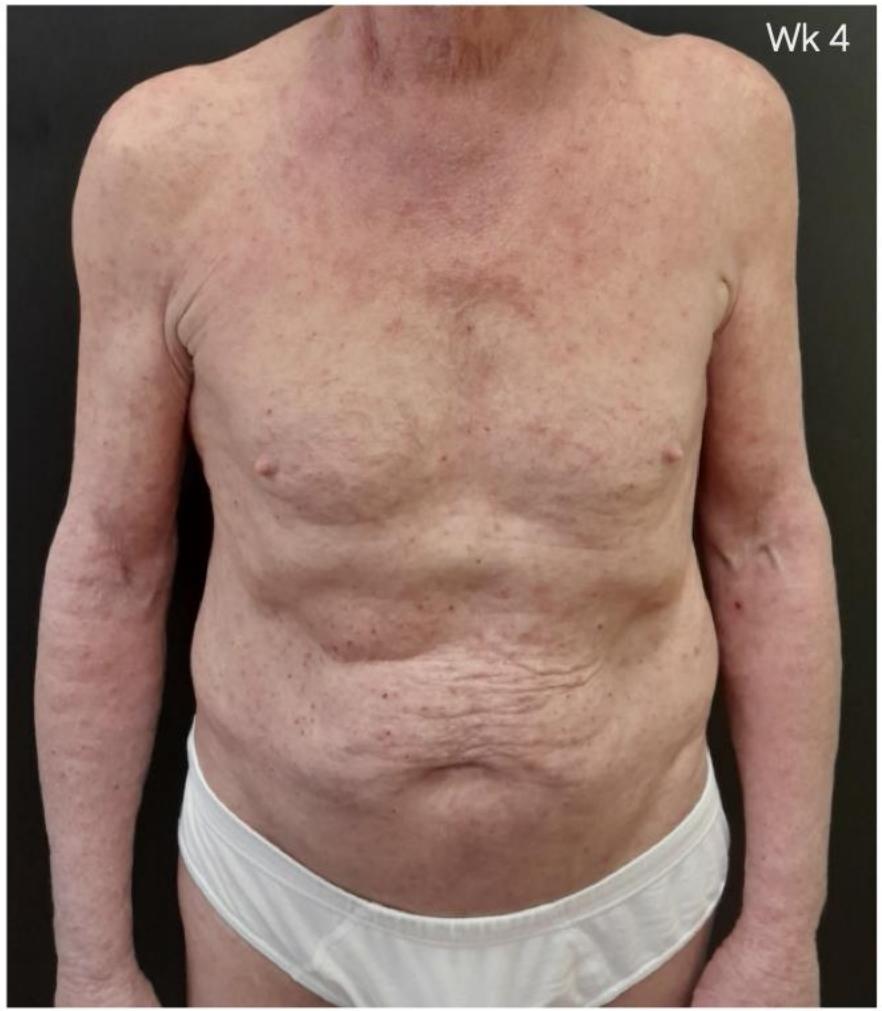
Clinical case: once you say yes, you never come back

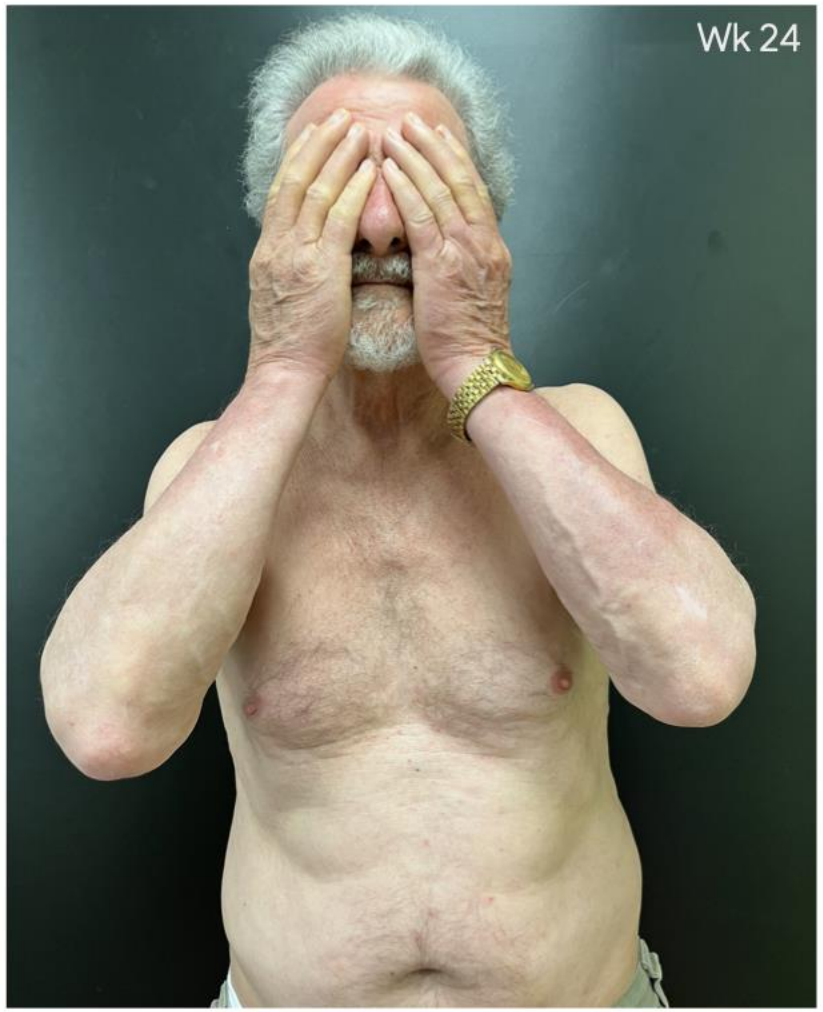


30% benzyl benzoate diluted in a sweet almond oil solution 300 ml applied once daily for 5 consecutive days

1. A. Giunta. Personal experience, for educational purpose only

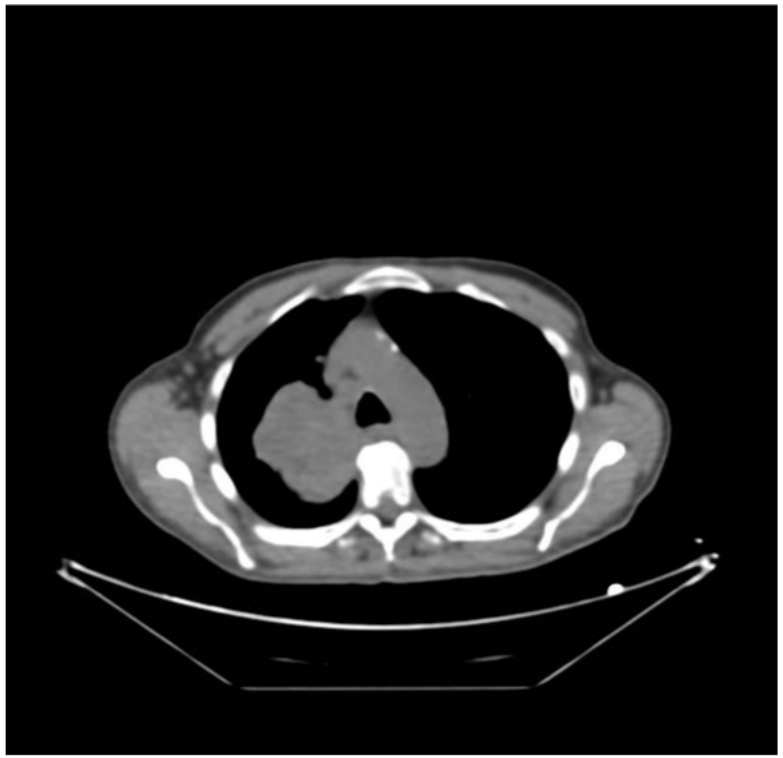
Clinical case: you wanted, it you got it





1. A. Giunta. Personal experience, for educational purpose only

Clinical case: consultation from the Oncology Unit



A 64-year-old white man was admitted in May 2023 for low back pain

CT abdomen revealed spine bone osteolytic lesions compatible with metastasis of an unidentified neoplasm

Subsequent CT-PET scan identified a voluminous neoformation (8×7 cm) in the upper lobe of the right lung and mediastinal lymphadenopathy

Trans-thoracic biopsy confirmed lung adenocarcinoma, therefore radiotherapy was initiated for D2-D5 and L3 vertebral lesions

In July 2023, positive (>50%) PD-L1 expression led to start Pembrolizumab therapy (200 mg i.v. every 3 weeks)

1. A. Giunta, C Di Raimondo. Personal experience, for educational purpose only

1. Le indicazioni terapeutiche del pembrolizumab sono il tumore al polmone ed il melanoma in stato avanzato?

1. SI
2. NO

European Medicines Agency [1]

Pembrolizumab EMA **indications**

① DERMATOLOGY

melanoma
head and neck squamous cell carcinoma (HNSCC)

② NEPHROLOGY

renal cell carcinoma
urothelial cancer

③ GASTROENTEROLOGY

oesophageal cancer
gastric and gastro-oesophageal junction adenocarcinoma
biliary tract cancer

④ HEMATOLOGY

classical Hodgkin lymphoma

⑤ PNEUMOLOGY

non-small cell lung cancer (NSCLC)

⑥ SENOLOGY

triple-negative breast cancer

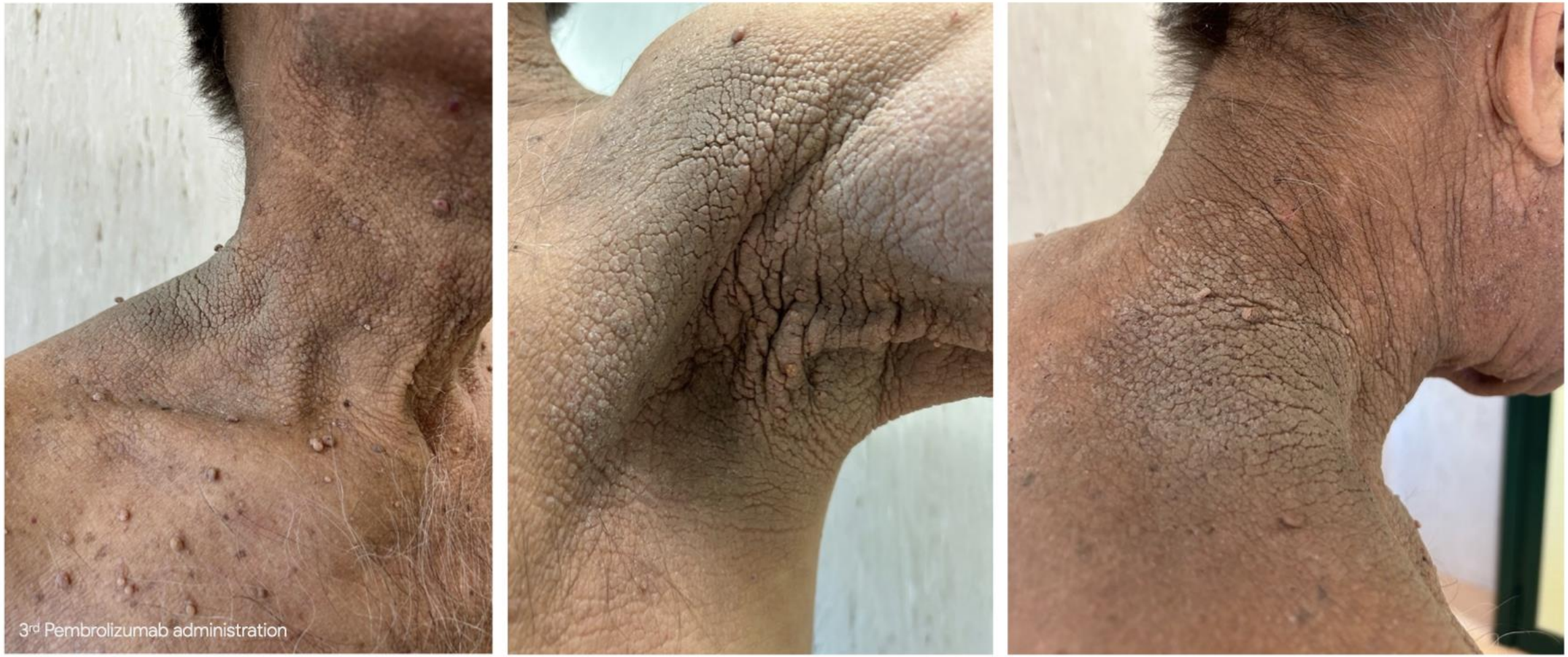
⑦ GYNECOLOGY

endometrial carcinoma
cervical cancer

Cancers when described as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR): colorectal cancer, endometrial carcinoma, gastric cancer, small intestine cancer, biliary cancer

1. https://www.ema.europa.eu/en/medicines/human/EPAR/keytruda

Clinical case: consultation from the Oncology Unit



1. A. Giunta, C Di Raimondo. Personal experience, for educational purpose only

1. L’Achantosis nigricans non è legata esclusivamente all’obesità

1. SI
2. NO

PER RISPONDERE collegati con il tuo smartphone a: meeter.it/yon

SCUOLA DERMATOLOGICA SERGIO CHIMENTI

Dermatology Update ROMA 17-18 Maggio 2024

YES or NO CONTEST 3° INCONTRO

Acanthosis nigricans pathophysiology and definition

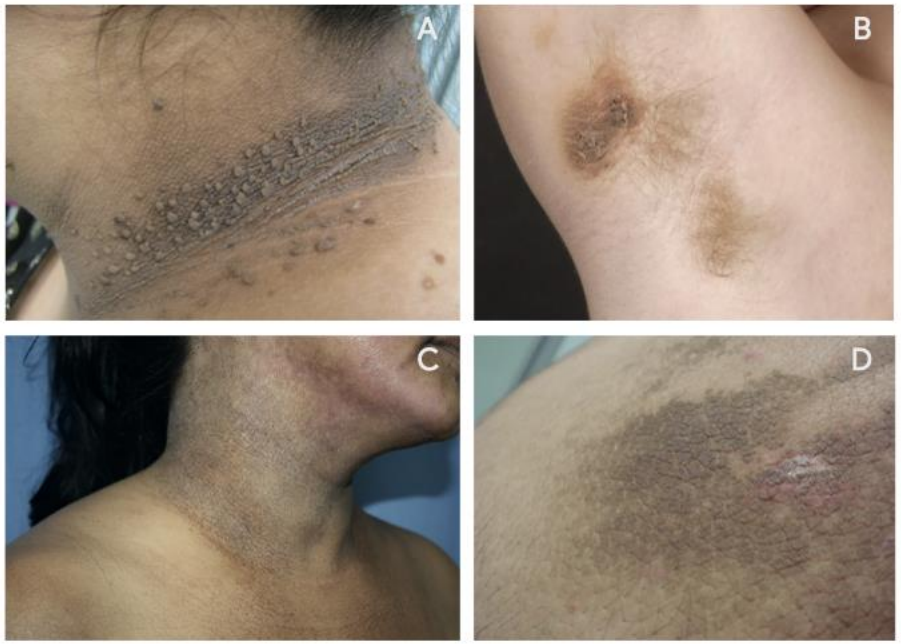


Figure 1. A) Achantosis nigricans B) Acanthosis nigricans form of epidermal nevus C) Atopic dirty neck D) terra firma-forme dermatosis

Acanthosis nigricans (AN) is described as a cutaneous disorder of multiple etiologies, characterized by symmetric, dark, coarse, thickened, velvety appearing plaques commonly distributed on the neck, axillae, antecubital and popliteal fossae, inframammary, and groin areas

The term was introduced by Paul Gerson Unna and the first case report was published by Sigmund Pollitzer in 1891

Morphologically similar cutaneous diseases may sometimes lead to diagnostic confusion. These include epidermal naevi, psoriasis, fungal infections, atopic dirty neck, confluent and reticulated papillomatosis, Hailey-Hailey disease, and terra firma-forme dermatosis

1. Das A, Datta D, Kassir M, Wollina U, Galadari H, Lotti T, Jafferany M, Grabbe S, Goldust M. Acanthosis nigricans: A review. J Cosmet Dermatol. 2020;19:1857-1865

Cutaneous findings in cases of morbid **obesity**

Skin manifestations in obese patients are quite diverse and include striae distensae, skin tags, plantar hyperkeratosis, acanthosis nigricans, the sequelae of hyperandrogenism, lymphedema, panniculus morbidus, chronic venous insufficiency, stasis dermatitis, leg ulceration, intertrigo, cellulitis, pressure ulcers and 'buried penis'. Obesity has also been associated with hidradenitis suppurativa, psoriasis, atopic dermatitis, systemic lupus erythematosus, lichen planus and acne vulgaris

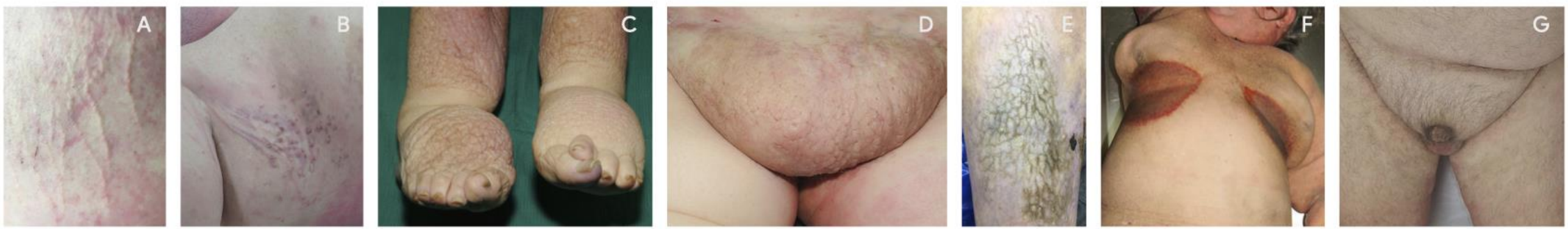


Figure 1. Clinical pictures of frequent skin manifestation in morbid obesity: A) Elevated striae in the lower abdomen B) A cluster of axillary skin tags C) Chronic lymphedema of the lower legs and feet D) Lymphatic obstruction of the fatty apron, so-called panniculus morbidus, with typical peau d'orange changes E) Violaceus discoloration with skin crusting and cracking in a case of chronic venous insufficiency F) Bilateral submammary reddened and moist areas of intertrigo G) A 'disappearing penis' being enveloped by pudendal fat

1. Byard RW. Manifestations and etiology of cutaneous findings in cases of morbid obesity. Forensic Sci Med Pathol. 2023 Oct 27
2. Uzuncakmak TK, et al. Cutaneous manifestations of obesity and themetabolic syndrome. Clin Dermatol. 2018;36:81-88
3. Hirt PA, et al. Skin changes in the obese patient. J Am Acad Dermatol. 2019;81:1037-1057

1. L'Acanthosis nigricans può essere un effetto collaterale del pembrolizumab?
2. SI
3. NO

Pembrolizumab safety: **skin disorders**

Skin and subcutaneous tissue disorders			
	Monotherapy	**In combination with chemotherapy**	**In combination with axitinib or lenvatinib**
Very common	pruritus [(a)], rash [(a)]	alopecia, pruritus [(a)], rash [(a)]	rash [(a)], pruritus [(a)]
Common	severe skin reactions [(a)], erythema, dermatitis, dry skin, vitiligo [(a)], eczema, alopecia, dermatitis acneiform	severe skin reactions [(a)], erythema, dermatitis, dry skin, dermatitis acneiform, eczema	severe skin reactions [(a)], dermatitis, dry skin, erythema, dermatitis acneiform, alopecia
Uncommon	psoriasis, lichenoid keratosis [(a)], papule, hair colour changes	psoriasis, vitiligo [(a)], papule	eczema, lichenoid keratosis [(a)], psoriasis, vitiligo*, papule, hair colour changes
Rare	Stevens-Johnson syndrome, erythema nodosum, toxic epidermal necrolysis	Stevens-Johnson syndrome, lichenoid keratosis [(a)], erythema nodosum, hair colour changes	toxic epidermal necrolysis, Stevens-Johnson syndrome

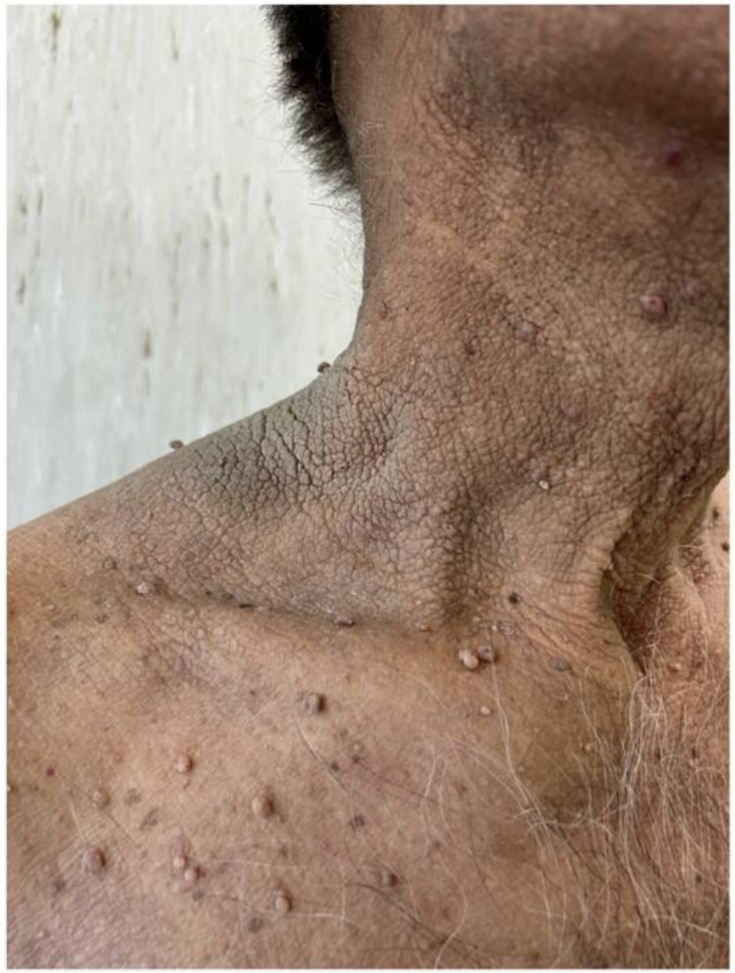
[(a)] *The following terms represent a group of related events that describe a medical condition rather than a single even*

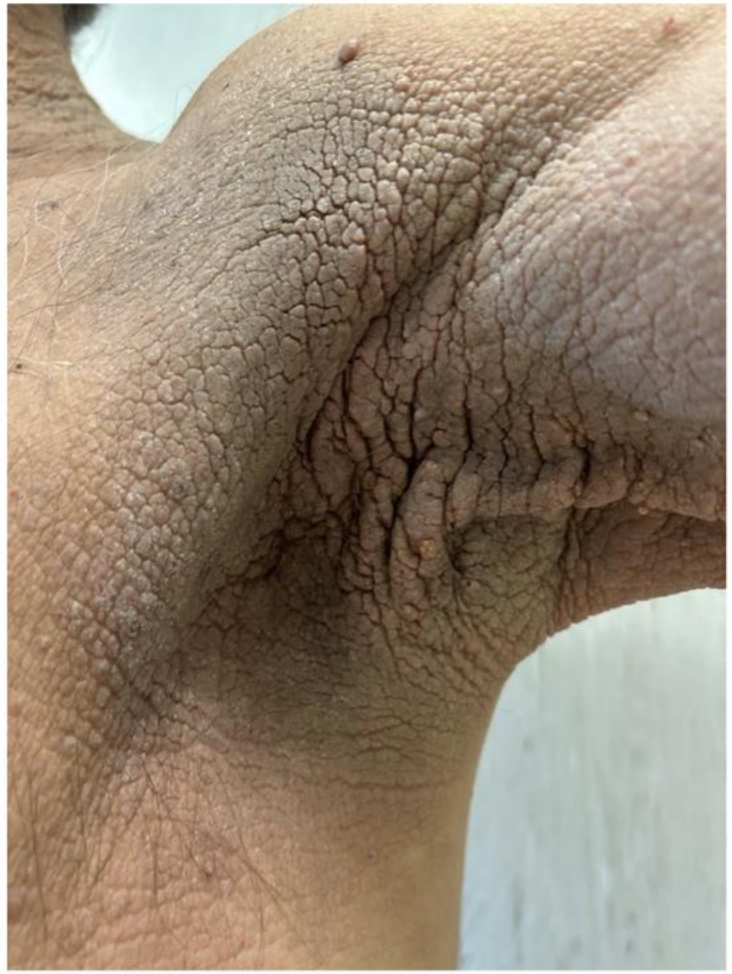
1. https://www.ema.europa.eu/en/medicines/human/EPAR/keytruda

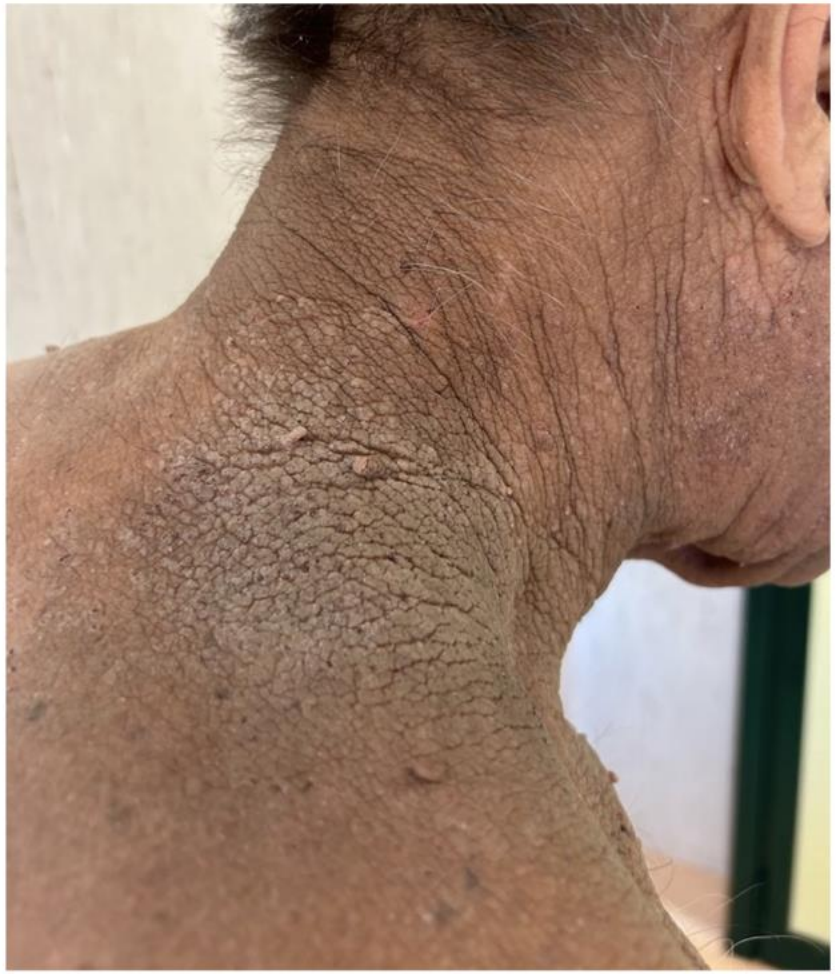
Acanthosis nigricans classification

Acanthosis Nigerians		
	Classification	**Reference**
Curth HO	A. Malignant B. Benign inherited C. Pseudo-associated with obesity D. Syndromic	Curth HO. Classification of acanthosis nigricans. Int J Dermatol. 1976;15:592-593
Hernández-Pérez E	A. Simple (including nevoid/obesity-related/drug related/ syndromic) B. Paraneoplastic	Hernández-Pérez E. On the classification of Acanthosis Nigricans. Int J Dermatol. 1984;23:605-606
Schwartz RA	A. Benign B. Obesity-associated C. Syndromic D. Malignant E. Acral F. Unilateral G. Medication-induced H. Mixed-type (when two varieties are present)	Schwartz RA. Acanthosis nigricans. J Am Acad Dermatol. 1994;31:1-19

Clinical case: consultation from the Oncology Unit







1. A. Giunta, C Di Raimondo. Personal experience, for educational purpose only

1. Le lesioni verruciformi nel contesto dell'acanthosis nigricans sono dovute all'immunosoppressione determinata dalla condizione oncologica?
2. SI
3. NO

PER RISPONDERE
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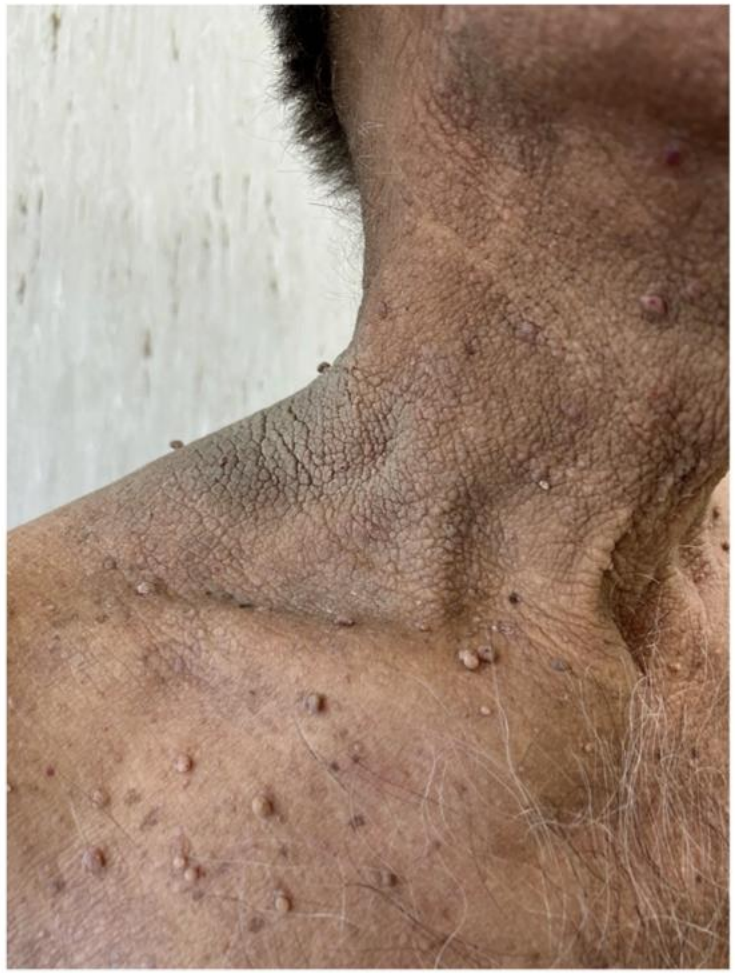
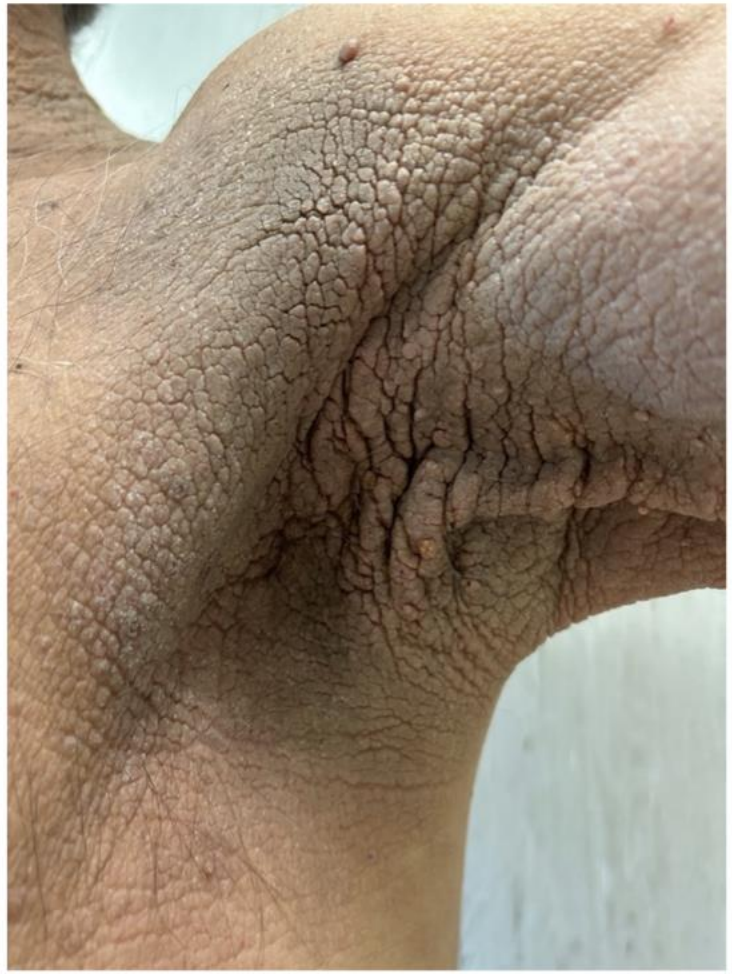
Clinical case: consultation from the Oncology Unit





A skin biopsy at the axillary site revealed hyperkeratosis of the epidermis, papillomatosis of the dermis, and irregular acanthosis

Immunohistochemical analysis for p16 and HPV-DNA detection excluded viral etiology

Considering the patient's underlying tumor and the characteristics of skin lesions, a diagnosis of paraneoplastic syndrome. After seven cycles of pembrolizumab, the patient's pulmonary neoplasm remains stable, with no improvement in the associated skin condition

1. A. Giunta, C Di Raimondo. Personal experience, for educational purpose only

PTV DERMATOLOGIA

Schwartz and Burgess syndrome or FCP

Florid Cutaneous Papillomatosis, Malignant Acanthosis Nigricans, and Pulmonary Squamous Cell Carcinoma

Patrick Gheeraert, M.D., Jean Goens, M.D., Robert A. Schwartz, M.D., M.P.H., W. Clark Lambert, M.D., Ph.D., Fabienne Schroeder, M.D., and L. Debusscher, M.D.

Abstract: *A 72-year-old man had florid cutaneous papillomatosis (FCP), which is an obligatory paraneoplastic syndrome always associated with an internal malignancy. The cancer, which is usually intraabdominal and most often gastric in origin, evolves parallel to the FCP. This patient is the first case of FCP occurring in association with a lung malignancy. An association of FCP with other signs of internal cancer is common, with malignant acanthosis nigricans usually appearing many times with the sign of Leser-Trélat. FCP, malignant acanthosis nigricans, and the sign of Leser-Trélat are part of a continuum, developing by a common or similar pathogenic pathway due to an underlying malignancy producing a factor possibly similar to human epidermal growth factor.*

Florid cutaneous papillomatosis (FCP) is a disease consisting of the rapid onset of numerous warty papules indistinguishable clinically from viral warts.[1–4] These lesions develop on the trunk and extremities. FCP has been described in association with malignant acanthosis nigricans and internal malignancy. We report a case associated with malignant acanthosis nigricans and a squamous cell carcinoma of the lungs.

Report of a Case

• A 72-year-old man was evaluated in December 1985 for the onset of multiple pruritic warty papules located predominately on the back of his hands and wrists, back, thighs, and knees of 3 months duration (Fig. 1). The papules gradually increased in size and number. He also noted fatigue, anorexia, and a weight loss of 12 kg in the previous year. Many years earlier he had a partial resection of the small bowel after a traumatic injury during an automobile accident. He also had a thyroidectomy. He smoked 20 cigarettes or more each day for over 50 years.

Physical examination showed the presence of multiple papillomatous verrucous lesions. The largest lesions were up to 1 cm in diameter and were indistinguishable from viral warts. The smallest of them were 2–3 mm in diameter. There was also a diffuse palmoplantar keratoderma (Fig. 2).

Multiple skin biopsies from these papillomas showed orthokeratotic hyperkeratosis, acanthosis, and papillomatosis (Fig. 3). There were no signs of viral inclusions or vacuolar degeneration of keratinocytes. Congo red staining was negative for amyloid. Ultrastructural microscopy also excluded the presence of viral inclusions and amyloid deposits. Papillomavirus serology was negative.

Initial laboratory evaluation was remarkable for a sedimentation rate of 50 mm/h, fibrinogen (538 mg/dl), C reactive protein (4.45 mg/dl), immunoglobulin G (2,075 mg/dl), and mottled ANA (1/2,500). A serum immunoelectrophoresis showed a monoclonal kappa component. Urinary sediment examination showed kappa and lambda light chain traces. Chest, skull, and upper gastrointestinal roentgenograms were normal at this time.

This first evaluation did not allow us to detect any internal malignancy despite a strong clinical suspicion and the suggestive paraneoplastic nature of the cutaneous lesions. The patient was interpreted as having only a benign monoclonal gammapathy. He was treated with etretinate 1 mg/kg/day for 1 month to improve his cutaneous hyperkeratotic lesions, but there was no benefit on the eruption or on his pruritus.

Six months later, in July 1986, the patient reappeared complaining of deteriorating health and mental depression. His skin lesions were unchanged, except for the onset of velvety brown hyperkeratotic papillomatous papules in the axillary folds typical of acanthosis nigricans (Fig. 4). His gammopathy remained stable, but his chest roentenogram, chest CAT scan, mediastinoscopy,

From the Departments of Dermatology, University Hospital Saint-Pierre, Brussels, Belgium, and New Jersey Medical School, Newark, New Jersey, and Institute J. Bordet, Brussels, Belgium. Address correspondence to: Robert A. Schwartz, M.D., Department of Dermatology, New Jersey Medical School, 185 South Orange Avenue, Newark, NJ 07103-2757.

Florid cutaneous papillomatosis with acanthosis nigricans in a patient with carcinomas of the lung and prostate

To the Editor: Acanthosis nigricans (AN) is a cutaneous finding characterized by velvety, hyperkeratotic plaques that predominate on flexural surfaces of the neck, axillae and groin.[1] Histologically, AN is characterized by papillomatosis and hyperkeratosis. When it is paraneoplastic it is called malignant AN. The onset of malignant AN may present with three other cutaneous signs: florid cutaneous papillomatosis (FCP), tylosis, and the sign of Leser-Trélat.[1,2]

A 70-year-old male presented in November 2003 for evaluation of multiple verrucous lesions on his hands, forearms, feet, and lower legs, which had developed since the summer of 2003. During that time he had also noticed a diffuse brownish hyperpigmentation and velvety thickening of the skin in the axillae, inguinal region, and mammillary areolae. He complained of generalized pruritus and weight loss of 5 kg within the last 3 weeks. The patient had ceased smoking 15 years earlier (15 pack years [a pack year being the number of years a patient has smoked cigarettes multiplied by the number of packs per day]) and was treated with allopurinol for hyperuricemia. Physical examination revealed numerous skin-colored firm and non-pendunculated, verrucous papules (0.5-1 cm in diameter) covering the dorsal region of his hands, wrists (Fig 1), and ankles as well as the dorsal aspects of the shins and calves. The plantar surfaces were spared. The skin of the axillae (Fig 2) and groin was thick, hyperpigmented, and velvety in appearance. His palms and soles were thickened and rough. Furthermore, tripe palms were noted.

Results of complete blood count, serum chemistry, and urinalysis were normal except for an increased level of creatinine 1.5 mg/dl (normal, <1.3 mg/dl), thyroid stimulating hormone 5.8 μU/ml (0.1–4 μU/ml), squamous cell carcinoma (SCC) antigen 40.1 ng/ml (<1.5 ng/ml), and prostate-specific antigen 7.68 ng/ml (<4.5 ng/ml). Serum levels for hemoglobin (11.7 g/dl), iron (30 μg/l), and transferrin (1.46 g/l) were decreased. Fasting plasma glucose levels were slightly impaired (100 mg/dl; normal <100 mg/dl). A computed tomography scan revealed a 7 cm × 7.2 cm mass infiltrating the middle and upper lobe of the right lung, enlarged hilar and pretracheal lymph nodes, and thickening of the pleural interstitium and enlargement of the prostate. Upper gastrointestinal endoscopy revealed diffuse papillomatosis of the esophagus (Fig 3).

Histologic examination of a wart-like skin lesion and a papillomatous esophageal lesion displayed pronounced hyperkeratosis, acanthosis, and papillomatosis. No evidence of human papilloma viral DNA was found by polymerase chain reaction.

SCC of the lung and adenocarcinoma of the prostate were confirmed by biopsy. Despite chemotherapeutic treatment with carboplatin and vinorelbine, no improvement of the SCC of the lung and the cutaneous lesions was observed, and the patient died 6 months later.

In general, malignant AN has a sudden onset with rapid spreading. Rarely it presents with other cutaneous and mucosal warty lesions (eg, CP).[1–3] In FCP, papillomas are most commonly located on the extremities, particularly on the backs of hands and wrists, but may disseminate to the entire body.[2] Furthermore, pachydermatoglyphy and intense

Fig 1. Flat wart or fibroma-like papules around the wrist, the dorsal area of the left hand, and forearm.

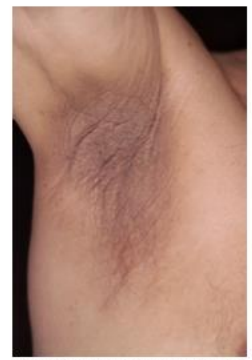


Fig 2. Acanthosis nigricans of the right axilla.

JEADV (2000) 14, 205–208

CASE REPORT

Florid cutaneous and mucosal papillomatosis with acanthosis nigricans revealing a primary lung cancer

Ugo Bottoni,* Caterina Dianzani, Guglielmo Pranteda, Daniele Innocenzi, Piero De Giacomo, Alberto Balzani, Maurizio Zampetti, Salvatore Pala, Stefano Calvieri

*Istituto di Dermatologia, Università di Roma 'La Sapienza', Viale del Policlinico 155, 00161 Roma, Italy. *Corresponding author, tel. +39 06 44740757; fax +39 06 4462104; E-mail: ubottoni@tiscalinet.it*

ABSTRACT

This is the report of an 80-year-old patient with diffuse brownish hyperpigmentation and velvety thickening of the skin with onset 1 year before. Warty lesions on his limbs were present as well as papillomatous and verrucous lesions on his lips, mouth and eyelid conjunctivae with hyperkeratosis of the nipples. Biopsies, performed at different sites, showed histological pictures consistent with a diagnosis of acanthosis nigricans (AN) with florid cutaneous and mucosal papillomatosis. This type of AN is frequently associated with internal malignancy. In our patient serum levels of tissue polypeptide antigen, carcinoembryonic antigen, cytokeratin fragment and squamous cell carcinoma antigen were high and chest computed tomography scan indicated a large tumour infiltrating the right lung and extending to the mediastinum. Cytological examination of bronchial drainage revealed the presence of neoplastic cells, non-small cell type carcinoma. The most frequent cancer associated with malignant AN is gastric adenocarcinoma. Lung tumour has rarely been reported with AN. Malignant AN is sometimes associated with other cutaneous and mucosal warty lesions, as in our patient. These various skin and mucosal lesions are the expression of a systemic epithelial disorder and may help clinicians to suspect a malignant form of AN.

Key words: acanthosis nigricans, cutaneous papillomatosis, mucosal papillomatosis, paraneoplastic syndrome

Received: 16 July 1999, accepted 3 April 2000

Introduction

Acanthosis nigricans (AN) is a disorder characterized by skin hyperpigmentation and thickening especially in certain regions, such as the neck, axillae and groins. This skin disorder may develop in response to metabolic or endocrinological diseases such as insulin-resistant diabetes mellitus, pituitary hypogonadism, Addison's disease, hypothyroidism, hyperandrogenic syndromes and obesity.[1] AN can be quite aggressive and spread all over the skin surface: verrucous papillomatous lesions may appear on the limbs, lips, mouth and eyelid conjunctivae. Some authors use the term florid cutaneous and mucosal papillomatosis to define these clinical pictures that are frequently paraneoplastic.[2–5]

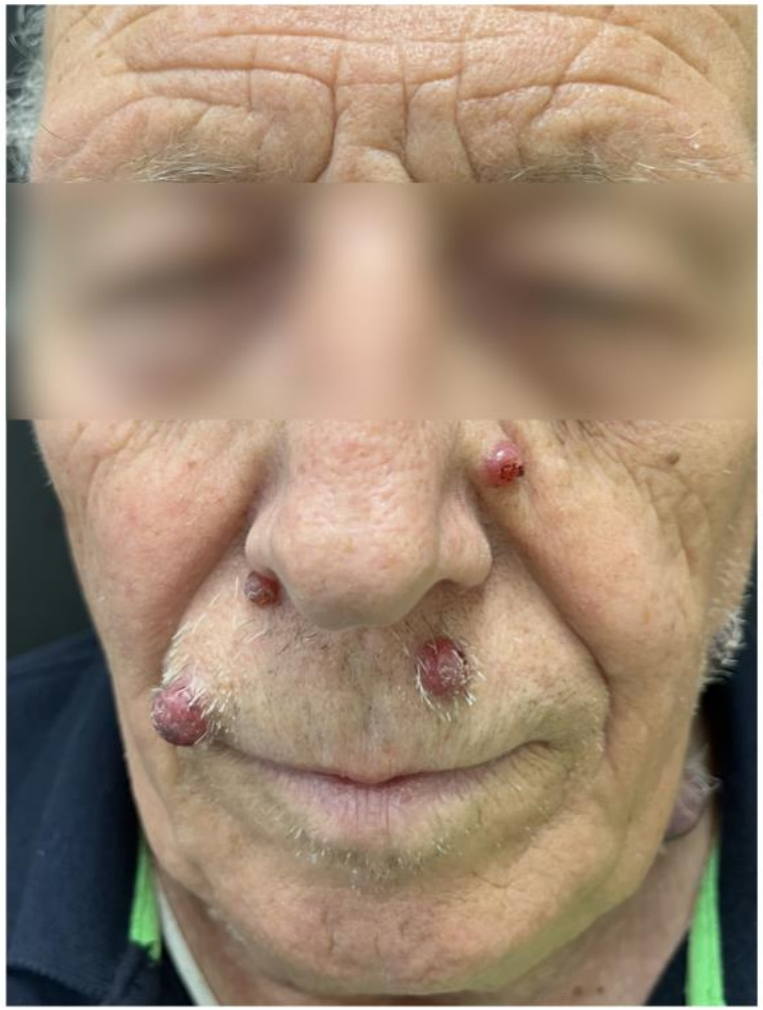
Recently, we saw an 80-year-old man affected by AN, with striking cutaneous and mucosal papillomatosis. Further examination revealed the presence of a pulmonary cancer.

Case report

In June 1997 an 80-year-old Caucasian patient was referred to our Institute of Dermatology at the University of Rome 'La Sapienza' for the presence of diffuse brownish hyperpigmentation and velvety thickening of the skin, associated with moderate itching. These cutaneous alterations had appeared 1 year before and were more evident on his neck, axillae and groins (fig. 1). There were also warty lesions on his upper and lower limbs and papillomatous and verrucous lesions on his lips, mouth and eyelid conjunctivae (fig. 2); also hyperkeratosis of the nipples was evident. The patient was under treatment with flecainide (100 mg/d) and acetylsalicylic acid (0.3 g/d) for blood hypertension and dysrhythmia. No systemic symptoms, including weight loss, were recorded, except for mild dyspnoea after exercise.

Ten years before this man had undergone partial resection

Clinical case: consultation from a Surgery Unit



76 years old man referred from a Emergency Surgery Unit of another Hospital for eruptive, vascular lesions arose in 3 weeks mainly on face, scalp and neck

Laboratory examination were within normal rages

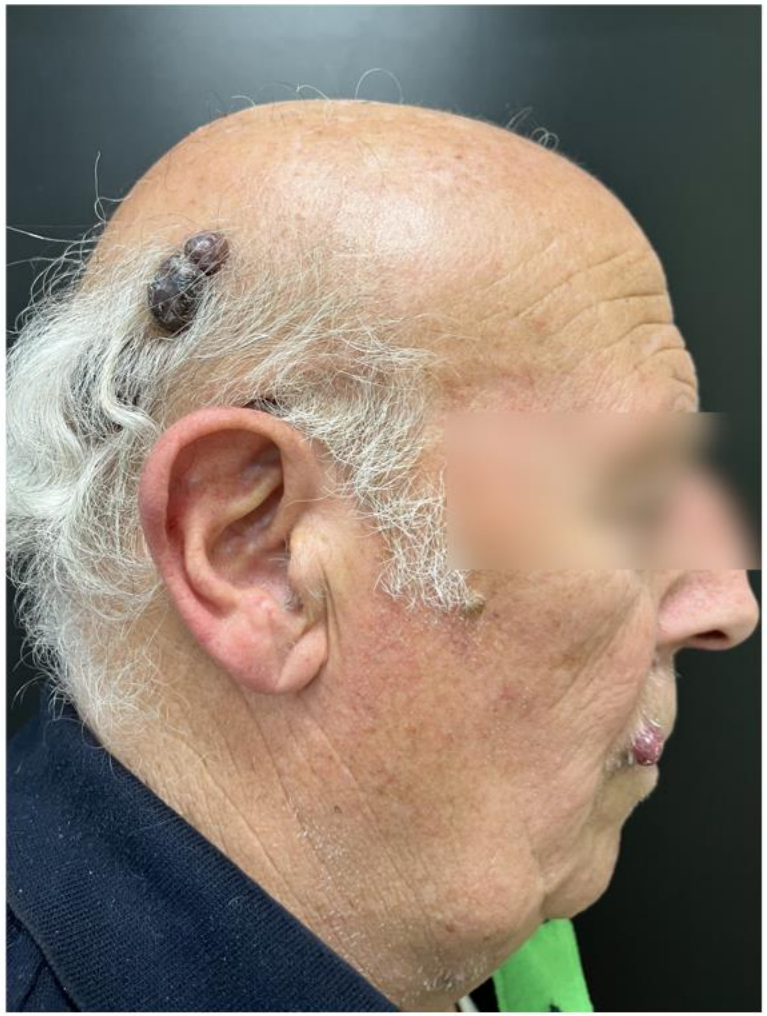
Negative for HBV, HIV, HBV, HCV

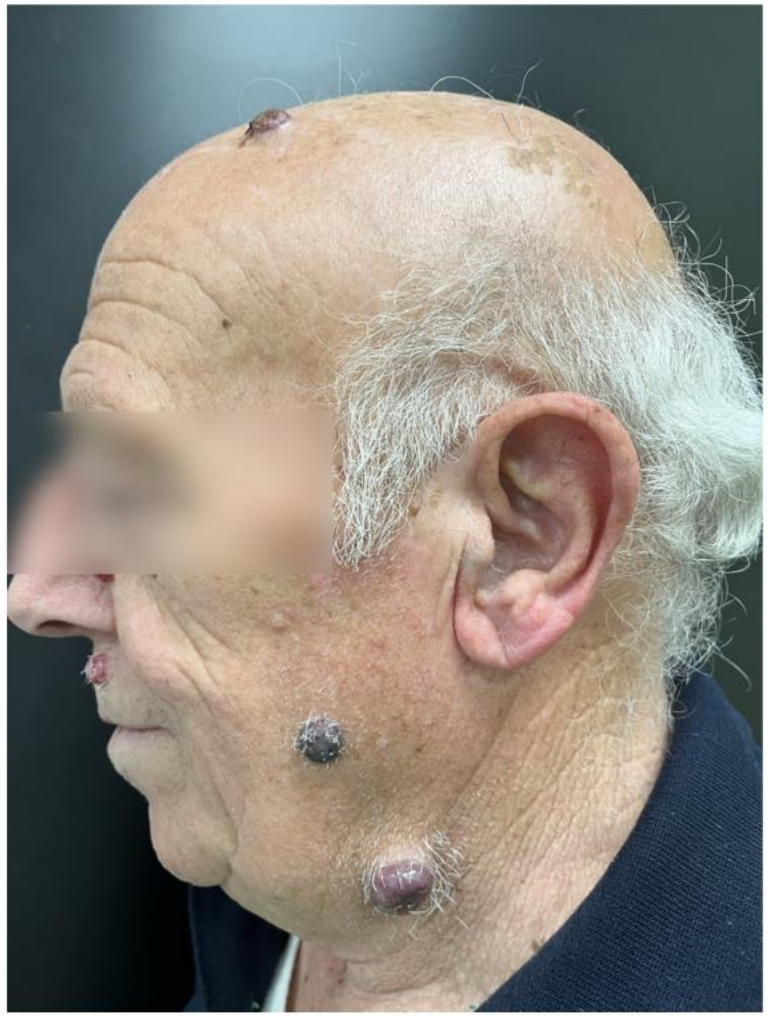
1 week before one of the lesion was excised for histologic examination

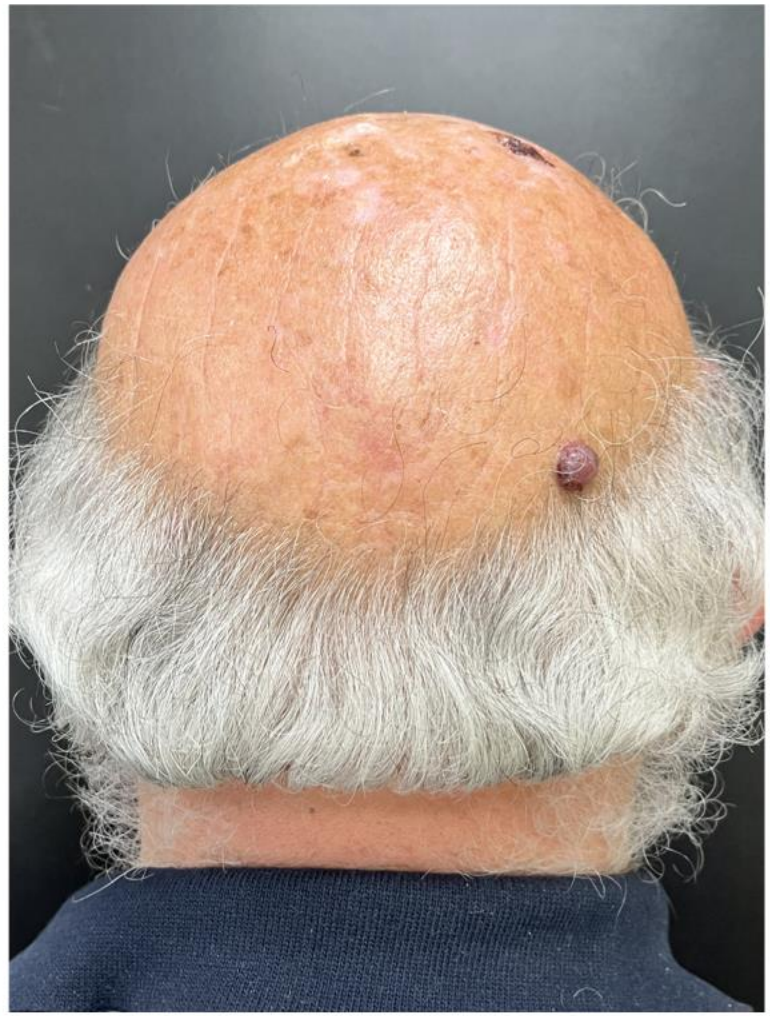
The patient referred the eruption linked to a laser ablation of a dermic nevus

1. A. Giunta. Personal experience, for educational purpose only

Clinical case: consultation from a Surgery Unit

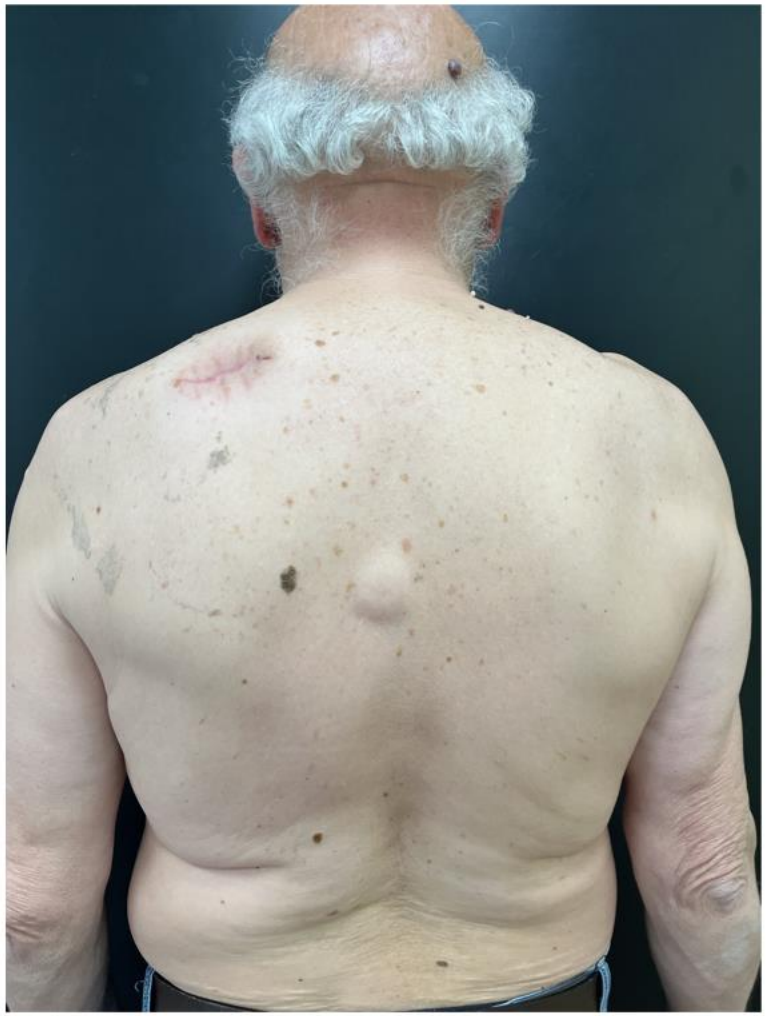


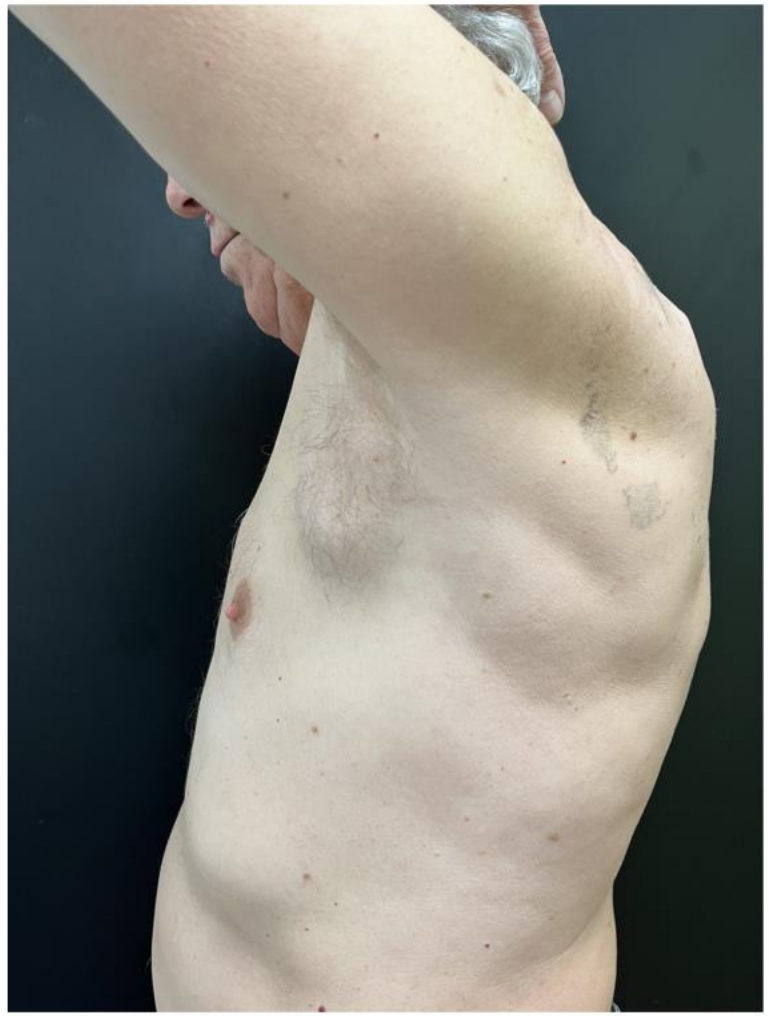




1. A. Giunta. Personal experience, for educational purpose only

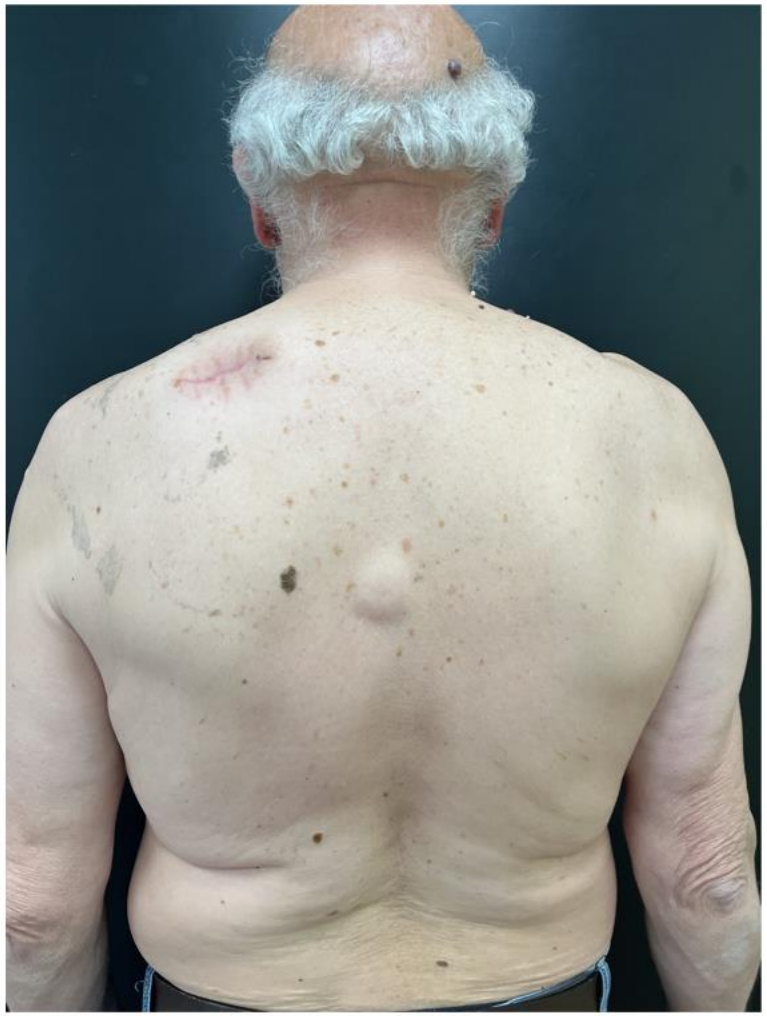
Clinical case: consultation from a Surgery Unit

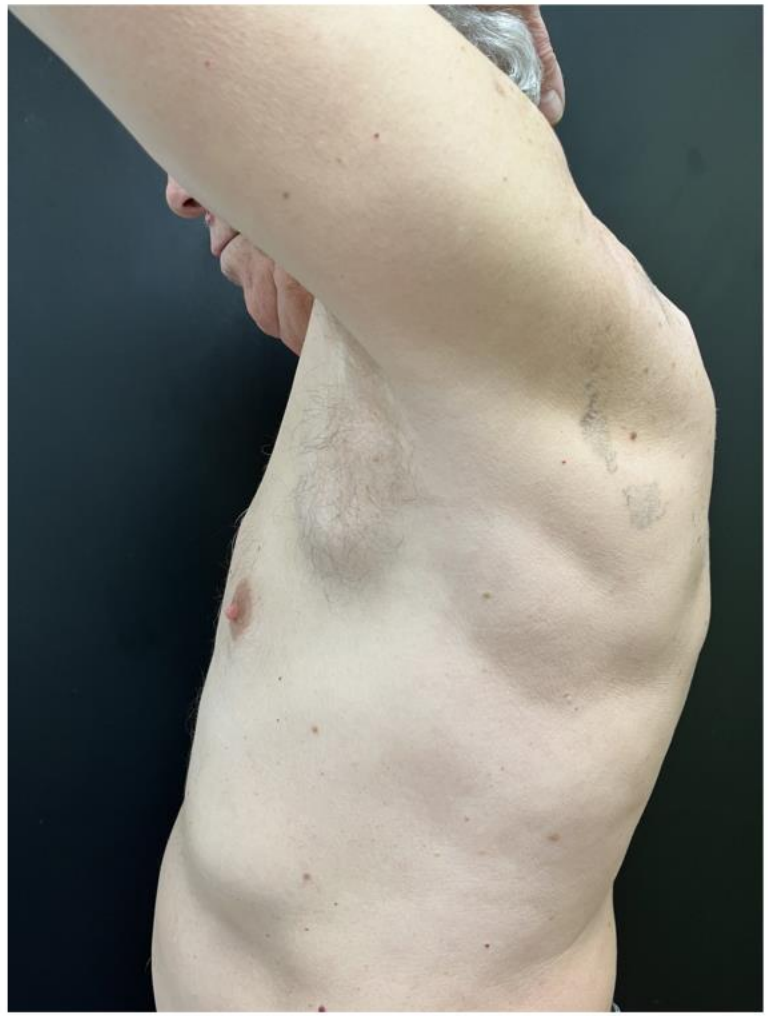


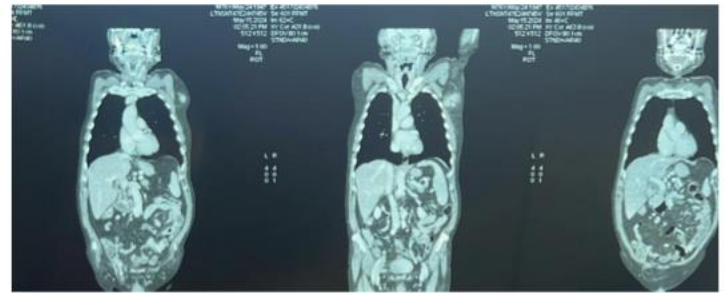


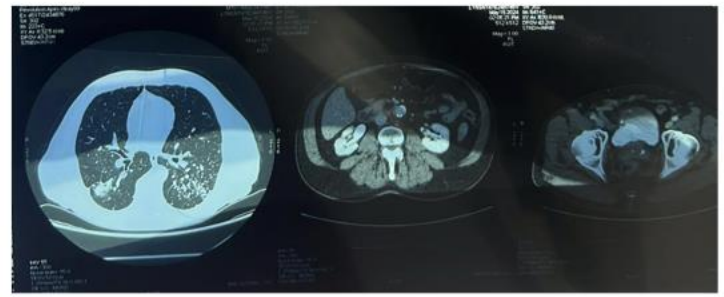
1. A. Giunta. Personal experience, for educational purpose only

Clinical case: consultation from a Surgery Unit









Nodular melanoma, non ulcerated, 4 mitoses/mm^2

Breslow: 11 mm, Clark: V

pT4aNxMx

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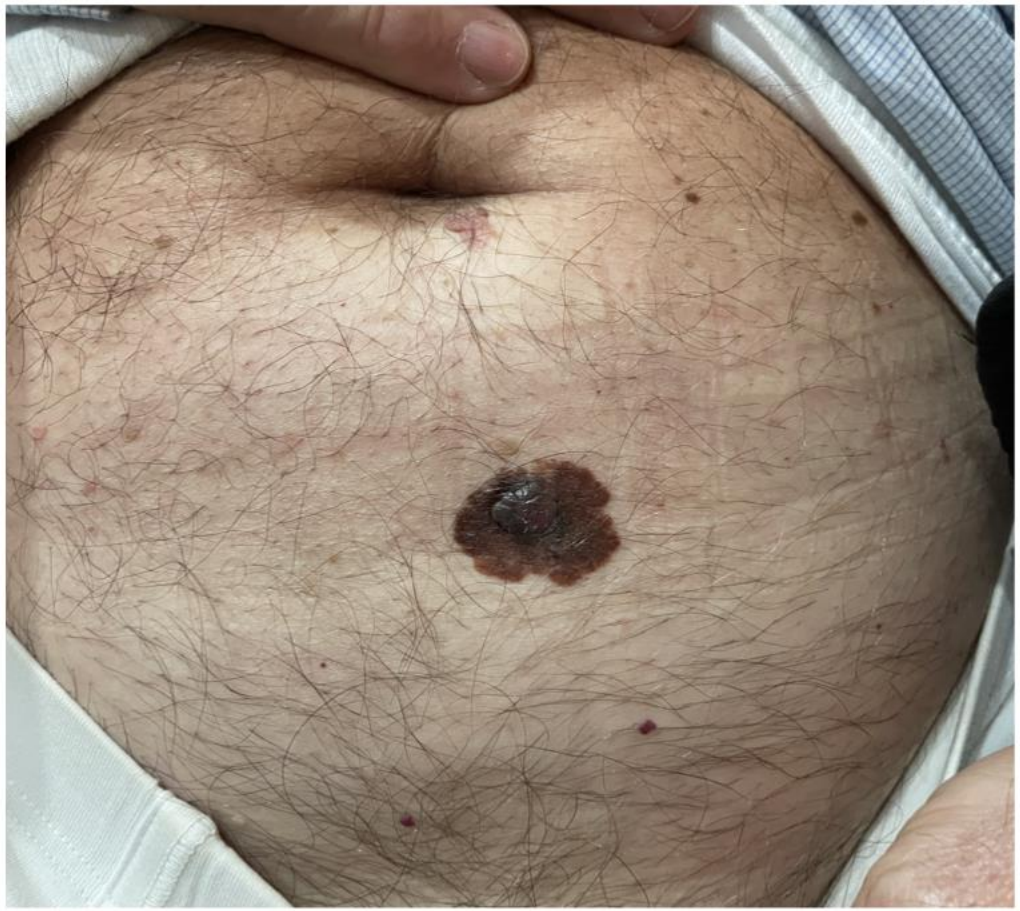
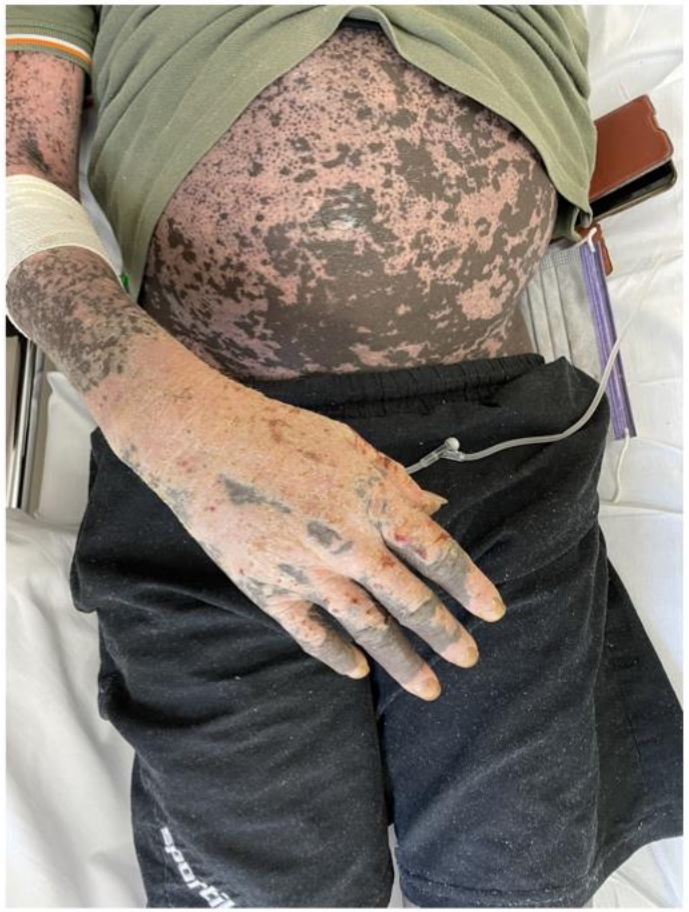
The **importance** of dermatological consultations





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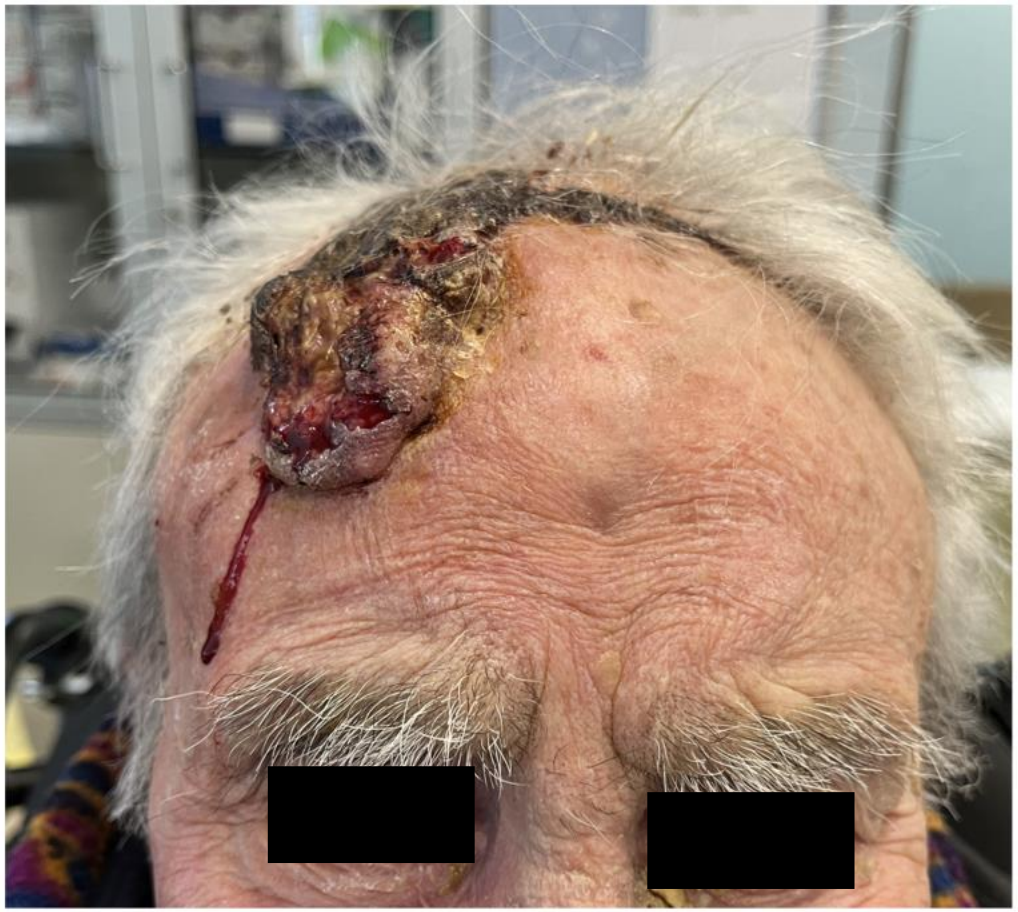
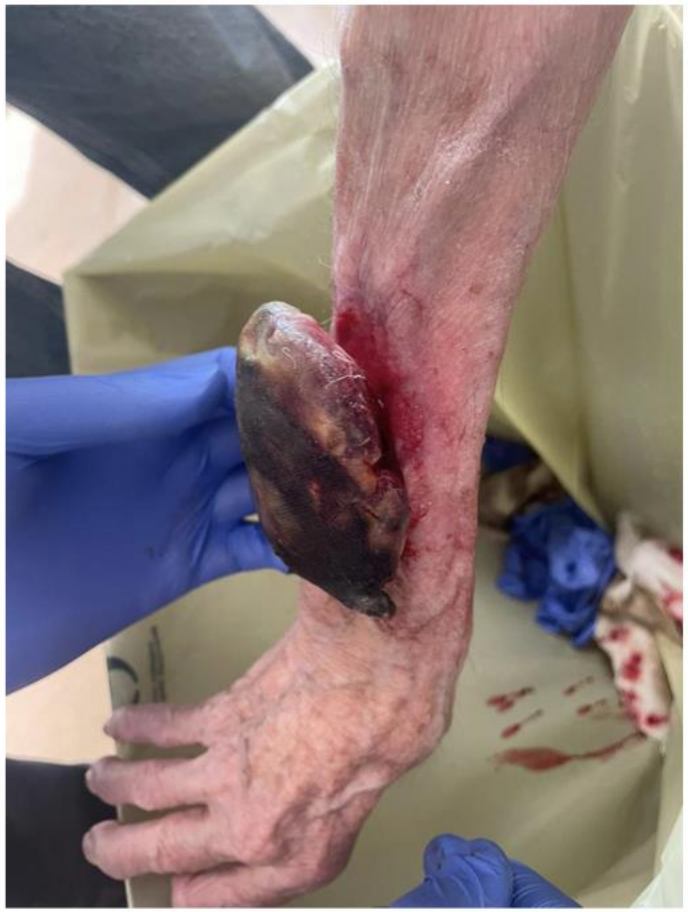
The **importance** of dermatological consultations





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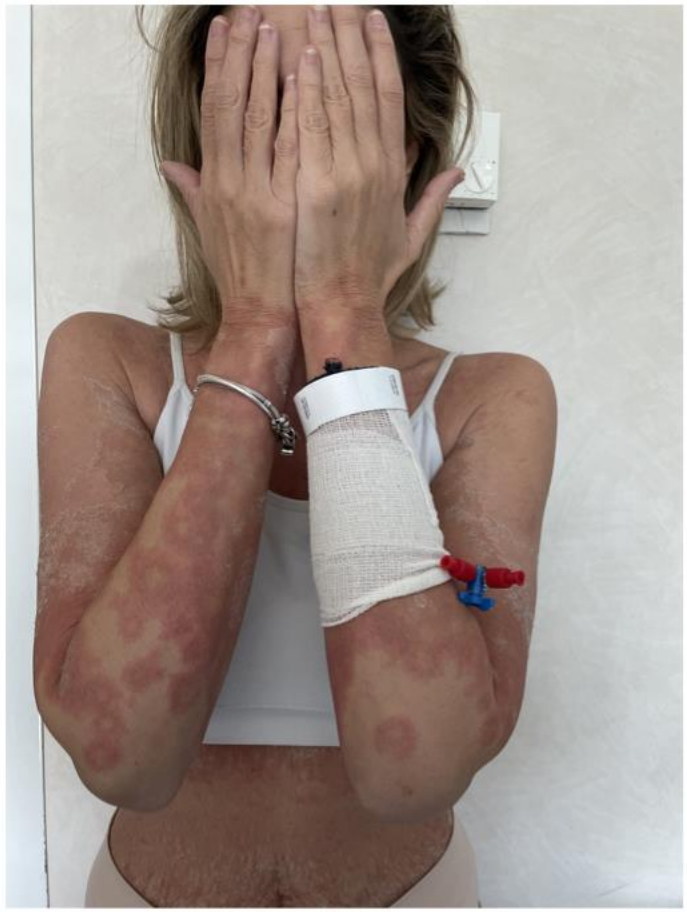
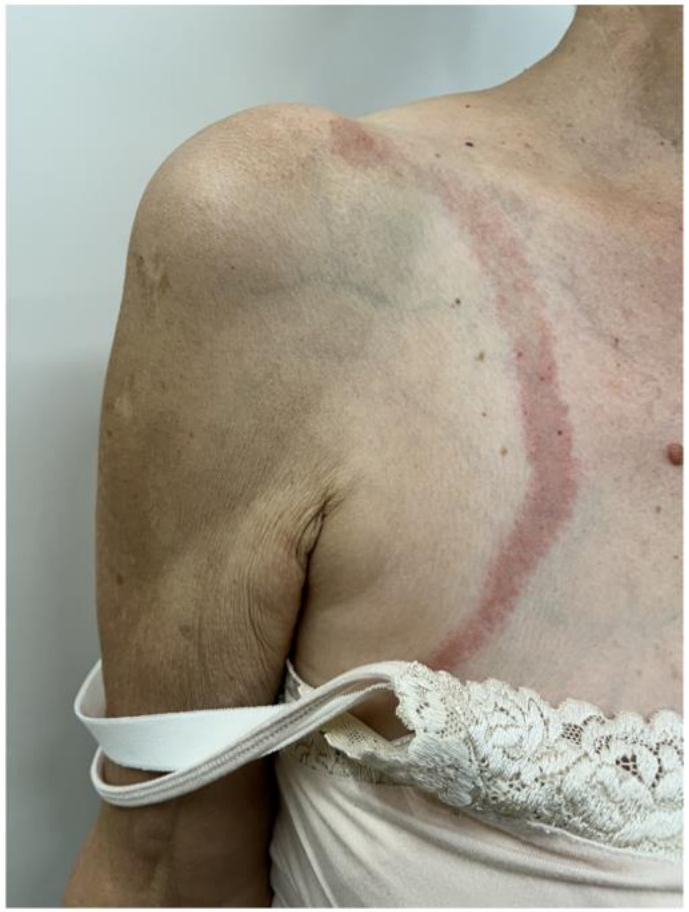
The **importance** of dermatological consultations





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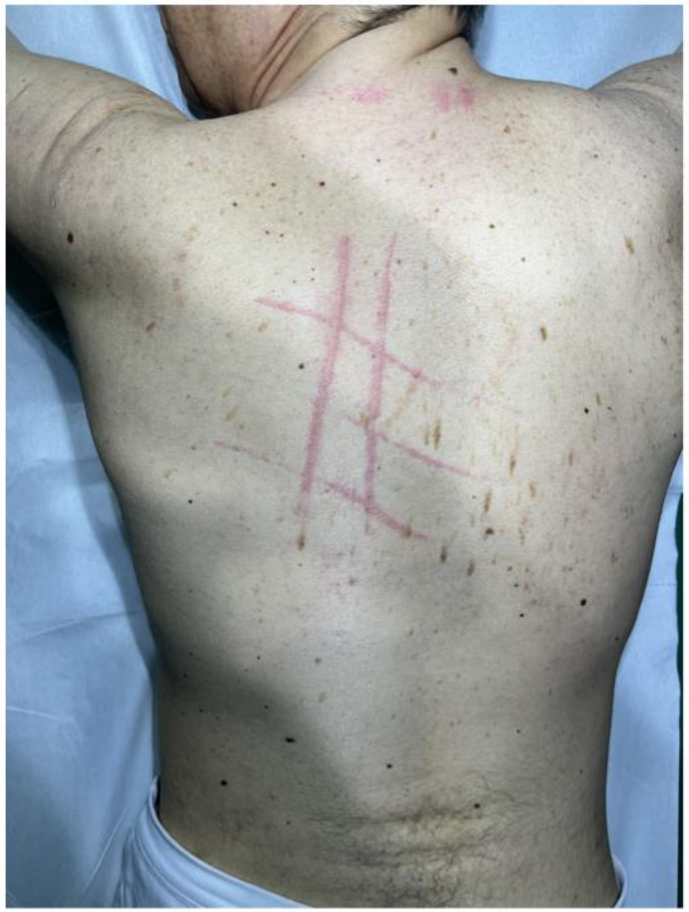
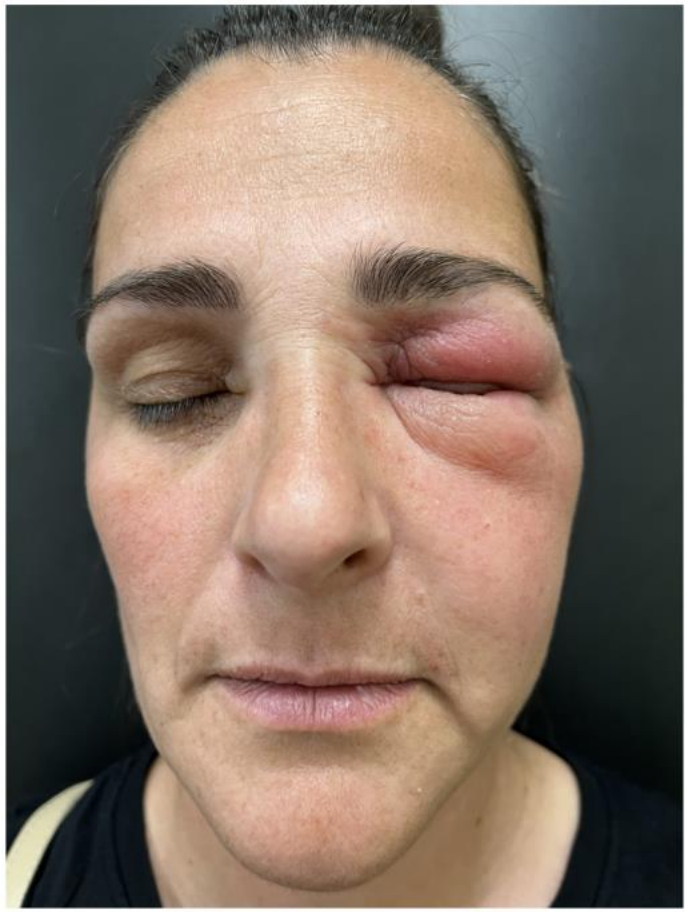
The **importance** of dermatological consultations





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DERMATOLOGIA

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