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Dermatological Manifestations Associated with Hereditary Renal Cell Carcinoma Syndromes – a systematic review

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DERMATOLOGICAL MANIFESTATIONS ASSOCIATED WITH HEREDITARY RENAL CELL CARCINOMA SYNDROMES – A SYSTEMATIC REVIEW

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Resumo

Introdução: Os carcinomas de células renais hereditários representam cerca de 3 a 8% dos carcinomas de células renais. Estas síndromes afetam todos os órgãos, sendo a pele o mais frequentemente atingido. A identificação destas lesões e consequentemente das síndromes permite a integração dos doentes e das suas famílias num programa de rastreio, diagnosticando e tratando o carcinoma de células renais o mais precocemente possível.

Objetivo: Destacar as manifestações dermatológicas das síndromes de carcinomas de células renais, sumarizando as restantes manifestações das síndromes.

Métodos: Foi realizada uma revisão sistemática da literatura com recurso ao *PubMed* e ao *Online Mendelian Inheritance in Man*, incluindo publicações desde janeiro de 2001 a abril de 2021. A nossa investigação focou-se no carcinoma de células renais hereditário com manifestações dermatológicas.

Seleção de estudo: Todos os títulos e resumos foram revistos e artigos com informação original acerca dos carcinomas de células renais hereditário com manifestações dermatológicas foram incluídos.

Resultados: As síndromes Birt-Hogg-Dubé, leiomiomatose hereditária e carcinoma de células renais, complexo esclerose tuberosa, tumor hamartoma-PTEN, predisposição tumoral BAP1, doença de von Hippel-Lindau e MiFT-associado a cancro foram identificadas e sumarizadas. As manifestações cutâneas mais frequentemente associadas ao carcinoma de células renais hereditário são fibrofoliculomas, tricodiscomas, piloleiomiomas, máculas hipomelânicas, angiofibromas, triquilemomas e tumores intradérmicos atípicos melanocíticos benignos associados à mutação BAP1. O carcinoma de células renais é frequentemente associado e tem uma histologia única reconhecida na classificação de tumores do rim da Organização Mundial de Saúde em 2016.

Limitações: A ausência de estudos baseados na população e meta-análises originais que fornecessem uma epidemiologia precisa e de critérios de diagnóstico que limitassem a inclusão destes doentes.

Conclusões: A afeção dermatológica é, na maioria dos casos, a primeira manifestação sindrómica, permitindo um excelente meio para o diagnóstico. Estas manifestações cutâneas podem ser pouco específicas, pois a mesma lesão pode ocorrer como parte de uma manifestação esporádica ou ser macroscopicamente similar a outra manifestação cutânea de uma genodermatose, ou ser a mesma manifestação cutânea de duas genodermatoses. Contudo, a associação destas lesões com a

neoplasia renal deve alertar o clínico para a presença de um síndrome hereditário com implicação no tratamento e seguimento destes doentes e seus familiares.

Palavras-Chave: Síndrome Birt-Hogg-Dubé, Leiomiomatose hereditária e carcinoma de células renais, Complexo esclerose tuberosa, Síndrome do tumor hamartoma-PTEN, Síndrome de predisposição tumoral BAP1, Doença de von Hippel-Lindau, Síndrome MIFT-associado a cancro, lesões cutâneas, síndrome de carcinoma de células renais hereditário

Abstract

Context: Hereditary renal cell carcinoma represents about 3 to 8% of all renal cell carcinomas. These syndromes affect all organs, being the skin one of the most frequently afflicted. The identification of these lesions and consequently these syndromes allows the integration of these patients and their families in a screening program, diagnosing and treating renal cell carcinoma as early as possible.

Objective: Outline the dermatologic manifestations on renal cell carcinoma syndromes, summarising the other syndromic features.

Data sources: A literature systematic review was performed using PubMed and Online Mendelian Inheritance in Man, including publications from January 2001 to April 2021. Our research focused on hereditary renal cell carcinoma with dermatological manifestations.

Study selection: All titles and abstracts were reviewed, and articles with original information about hereditary renal cell carcinoma with dermatological features were included.

Data synthesis: Birt-Hogg-Dubé syndrome, hereditary leiomyomatosis and renal cell cancer, tuberous sclerosis complex, PTEN hamartoma tumour syndrome, BAP1 tumour predisposition syndrome, von-Hippel Lindau syndrome, and MiTF-associated cancer syndrome, have been identified and summarised. The skin manifestations most frequently associated with hereditary renal cell carcinoma are fibrofolliculomas, trichodiscomas, piloleiomyomas, hypomelanotic macules, skin angiofibromas, trichilemmomas and melanocytic BAP1-mutated atypical intradermal tumours. Renal cell carcinoma is also prevalent, and has a unique histology, recognised by World Health Organization classification of tumours of the kidney in 2016.

Limitations: Limited original population-based studies and meta-analysis providing an accurate epidemiology and the absence of diagnostic criteria limiting the inclusion of these patients on the population-based studies and meta-analysis.

Conclusions: Dermatological afflictions are in most cases, the first syndromic manifestation, providing an excellent vehicle for diagnosis. This skin manifestations can be nonspecific as the same lesion can occur as part of a sporadic nonsyndromic manifestation or have a macroscopic appearance similar to other syndromic features, or the same manifestation can occur in a different genodermatosis. However, the association of these lesions with kidney cancer should alert the clinician to the presence of a hereditary syndrome, which have implications in treatment and follow-up of the patients and their family members.

Keywords: Birt-Hogg-Dubé syndrome, Hereditary leiomyomatosis and renal cell cancer, Tuberous sclerosis complex, PTEN hamartoma tumour syndrome, BAP1 tumour predisposition syndrome, von Hippel-Lindau syndrome**,** MIFT-associated cancer syndrome, skin features, hereditary renal cell carcinoma syndrome

List of Abbreviations

AST – Atypical Spitz tumour

BAP1-TPDS – BRCA-1 associated protein-1 tumour predisposition syndrome

BHD – Birt-Hogg-Dubé

BHDS – Birt-Hogg-Dubé syndrome

ccRCC – Clear cell renal cell carcinoma

CNS – Central nervous system

CT – Computed tomography

FH – Fumarate hydratase

FLCN – Folliculin gene

HLRCC – Hereditary leiomyomatosis and renal cell carcinoma

HOCT – Hybrid oncocytic/chromophobe tumours

HRTS – Hereditary renal tumour syndromes

IP3R3 – Inositol-1,4,5-triphosphate receptor type 3

MBAIT – Melanocytic BAP1-mutated atypical intradermal tumour

MiTF – Microphthalmia-associated transcription factor

MRI – Magnetic resonance imaging

mTOR – Mammalian target of rapamycin

mTORC1 – mTOR complex 1

NEMMP – Naevoid melanoma-like melanocytic proliferation

OMIM – Online Mendelian Inheritance in Man

PTEN – Phosphatase and tensin homolog

PHTS – PTEN hamartoma tumour syndrome

RCC – Renal cell carcinoma

Rheb-GTP – GTPase Ras homolog enriched in brain

SHOCT – Sporadic hybrid oncocytic/chromophobe tumours

TSC – Tuberous sclerosis complex

US – Ultrasound

VEGF – Vascular endothelial growth factor

VHL – von Hippel-Lindau

VHLS – von Hippel-Lindau syndrome

WHO – World Health Organization

YAG – Yttrium aluminium garnet

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Introduction

Renal cell carcinomas (RCCs) are part of a heterogenous group of renal carcinomas rising from the renal parenchyma.[1, 2] The incidence of these adenocarcinomas has been increasing in the past 20 years in developed countries due to the extensive use of diagnostic exams. Recent research has shown a trend towards the plateau in the incidence of these carcinomas and a slight decrease in mortality. European statistics have shown an incidence of RCC around 2-3%.[2, 3] Even though these carcinomas are mostly sporadic, 3 to 8% have a hereditary component, which may be underestimated.[4, 5] Although there are some well-recognised characteristics such as early onset age (≤ 46 years old), multifocality and bilaterality, typical histological patterns and specific extra-renal manifestations[1, 6], this identification is still a challenge for the clinician. The penetrance of these hereditary syndromes is, in most cases, incomplete, and the manifestations may not affect all generations. In addition, some are de novo mutations and features such as multifocality and extra-renal manifestations may only occur on follow-up.[7, 8] Currently, there are no specific guidelines that recommend which patients should be screened for hereditary renal cell carcinoma syndromes.[8, 9] It is up to the physician to recognize these syndromes and guide those who might benefit from genetic counselling.

Of the manifestations present on renal cell carcinoma syndromes, the skin is one of the most frequently affected organs. These syndromes can be well-identified genodermatosis and phakomatosis such as Birt-Hogg-Dubé syndrome, PTEN hamartoma tumour syndrome, Tuberous sclerosis complex and Hereditary leiomyomatosis and renal cell carcinoma, or emerging syndromes with skin abnormalities. The identification of these skin lesions and consequently these syndromes allows the integration of these patients and their families in a screening program, providing early diagnosis and treatment of renal cell carcinoma. To date, ten hereditary renal tumour syndromes (HRTS) have been identified.[6] Seven of which present with skin manifestations and are systematised in table I.

The aim of this systemic review is to outline the dermatologic manifestations of hereditary renal cell carcinoma syndromes, summarising the syndromic features and rendering them easier to be recognised by the clinicians.

Methods

A systematic literature search was performed applying a combination of keywords (MeSH terms and free words) including: hereditary renal cell carcinoma syndrome, skin features, Birt-Hogg-Dubé syndrome, Hereditary leiomyomatosis and renal cell cancer, Tuberous sclerosis complex, PTEN hamartoma tumour syndrome, BAP1 tumour predisposition syndrome, von Hippel-Lindau syndrome, MIFT-associated cancer syndrome on PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Online Mendelian Inheritance in Man (OMIM) (https://www.ncbi.nlm.nih.gov/omim/). Our research was limited to include publications between January of 2001 and April of 2021, in English. We found 946 articles. All references were logged in Endnote reference management software, and duplicates were removed. All titles and abstracts were reviewed, and articles were eligible for inclusion if they contained relevant original information on dermatological manifestations associated with familial kidney cancer syndromes. After review 78 articles were deemed acceptable and included. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram is shown on fig 1[10].

Furthermore, databases from *Centro Hospitalar Universitário do Porto* were searched to identify clinical cases of hereditary renal cell carcinoma syndromes to document the dermatological lesions. After informed consent, these cases were reviewed, and the cutaneous lesions photographed.

Results

Birt-Hogg-Dubé syndrome

Birt-Hogg-Dubé syndrome (BHD; Online Mendelian Inheritance in Man #135150), or Hornstein-Knickenberg syndrome is a genodermatosis with an autosomal dominant transmission and extracutaneous manifestations such as lung cysts, pneumothorax and RCCs. It was first identified in 1975 by Hornstein and Knickenberg while studying perifollicular fibromas in two siblings. In 1977, Birt and colleagues observed a family with the same skin features, designating them cutaneous fibrofolliculomas, as well as trichodiscomas and acrochordons. Only posteriorly, it was associated with kidney tumours, pulmonary cysts, and recurrent spontaneous pneumothorax.[11-13]

The incidence of Birt-Hogg-Dubé syndrome (BHDS) is still uncertain. Presentation varies from patient to patient and even between family members, including phenotypes with only renal cell carcinoma or pneumothorax. Besides, 25% of patients with the diagnosis of Birt-Hogg-Dubé syndrome do not have skin manifestations by the time of diagnosis.[14, 15]

The triad of fibrofolliculomas, trichodiscomas and acrochordons described by Birt et al usually develops around thirty to forty years old, although some milder phenotypes can occur later.[15] Almost 90% of BHDS carriers have skin manifestations throughout their lives.[11] These lesions are typically the first manifestation of the syndrome affecting more men[15] and having a lower prevalence in Asian population, as they are usually smaller and can go unnoticed.[16-18] Fibrofolliculomas and trichodiscomas are specific but not pathognomonic of BHDS. These cutaneous manifestations are characterised by small (2-4 millimetres), dome-shaped, yellowish, or skin-coloured papules, usually affecting the face, neck, and the upper torso and are not distinguishable to the naked eye. Histologically, fibrofolliculomas are folliculo-sebaceous hamartomas resulting from mesodermal and ectodermal parts and trichodiscomas are originated from pilosebaceous mesenchyme. The difference between them resides on the fact that fibrofolliculomas have a larger epithelial prominence. Some authors consider that they are different temporal stages of the same lesion.[15] Acrochordons, also known as skin tags, are pedunculated papules or tumours that are prevalent in general population. It has been argued that these genetic acrochordons are histologically different from nonsyndromic acrochordons being a variation of fibrofolliculoma and trichodiscoma.[14, 15, 19] Recent research has also associated angiofibromas as a feature of BHDS,[20] constituting tuberous sclerosis complex a differential diagnosis.[21]

Thirty-four percent of patients with BHDS will develop renal cell carcinoma. The late onset age, between 48 to 51 years old may be a challenge on the syndromic diagnosis.[17, 22] Moreover, characteristics such as multifocality and bilaterality may not be present by the time of diagnosis.

Pathologists have a central role in diagnosing this syndromic feature since histologic features of BHDS renal carcinoma are rare, being either hybrid oncocytic/chromophobe tumours (HOCT) (50%) or chromophobe RCC (34%).[6] According to World Health Organization (WHO), HOCT are categorised as a subtype of chromophobe RCC. It is regarded as an overlap between the histology of an oncocytoma and a chromophobe RCC. It is important to highlight that HOCT is rarely associated with sarcomatoid features, in comparison with the sporadic chromophobe RCC. Furthermore, it has been reported an increased risk of developing clear cell RCC, papillary RCC and angiomyolipoma in BHDS.[17]

More than 80% of patients with BHDS have multiple and bilateral pulmonary cysts and a 50 times higher risk of spontaneous pneumothorax.[15, 22]

In 2002, germline mutations encoding folliculin (FLCN) gene between exons 4 and 14 located in 17p11.2 were linked to Birt-Hogg-Dubé syndrome. It is believed that the mutation on FLCN follows the Knudson's two-hit model. The causative association between these mutations and the cutaneous and extra-cutaneous manifestations is far from being understood. It is argued that the oncogenic features result from an increase on HIF-1α and WNT signalling pathway activity.[12, 23] However, the incidence of these carcinomas later in life reinforces the premise that kidney cancer can form from a benign precursor. When it comes to pulmonary cysts genesis, it seems to be explained by a ciliary defect. [24]

Diagnostic criteria for BHDS, outlined in table II, are based on clinical manifestations and genetic testing. It is now understood that this syndrome has a broad clinical spectrum. That said, patients with early renal cancer onset, multifocal or bilateral disease, and HOCT or chromophobe histology, unexplained cystic lung disease, pneumothorax, family history of cystic lung disease or pneumothorax, familial renal cancer or positive family member for the disease should be offered genetic testing to confirm the diagnosis.[15, 25] Additionally, sporadic presentation forms of HOCT (SHOCT) without the identification of the FLCN coding exons should not exclude BHDS as the identification of the folliculin gene may not occur in 7-9% of patients.[15, 17]

Management of Birt-Hogg-Dubé syndrome should be discussed with the patient. The alternative options available for skin features are temporary and include laser ablation with an Erbium-YAG (yttrium aluminium garnet) and fractional carbon dioxide laser. Since these patients have a higher risk of developing kidney cancer, annual surveillance should be performed, starting at 20 years old with magnetic resonance imaging (MRI) or ultrasound (US), if MRI is not available, should be performed. If suspicious tumours larger than 3 centimetres are detected, nephronsparing surgery

is the recommended treatment. If patient's history includes spontaneous pneumothorax the recommendation is to reference to a pulmonologist.[15, 25]

Hereditary leiomyomatosis and renal cell cancer

The association between uterine and cutaneous leiomyomata was first noticed in 1954 by Blum and Jean. It was only in 1973 that Reed and colleagues noticed a dominant inheritance pattern in two families with these features, designating it by Reed's syndrome. After the association with RCC in 2001, this syndrome was renamed to Hereditary leiomyomatosis and renal cell cancer (HLRCC; Online Mendelian Inheritance in Man #150800).[26, 27]

The epidemiology is still not known, although some studies report about 200 to 300 families affected worldwide, which represents a prevalence of approximately 1 to 200 000. [28, 29]

The responsible gene mutation for this syndrome was first identified in 2002 on chromosome 1 (1q43), encoding fumarate hydratase (FH) enzyme, which involves the tricarboxylic acid cycle, also known as Krebs cycle, and DNA damage response pathway. This mutation has an autosomal dominant inheritance pattern and follows the two-hit hypothesis. It is thought that tumorigenesis results from intracellular accumulation of fumarate which in place can inhibit prolyl hydroxylase and generate reactive oxygen species leading to a pseudohypoxia state.[30] It is important to highlight that this disease is one of the few in which the inheritance of either one or two copies results in two different phenotypes. As so, the inheritance of two allele mutation results in fumarate hydratase deficiency, manifesting neonatally or in early childhood and characterised by encephalopathy, neurologic abnormalities and difficult to thrive. In addition, research has shown cutaneous leiomyomas in parents of children with this disease. [31, 32]

Skin leiomyomatosis is the first manifestation of HLRCC, affecting 78% of individuals with this diagnosis, throughout their lives.[29] Ranging from one to more than one hundred and fifty lesions, they tend to increase in size and number as patients get older. The cumulative risk for the development of these skin lesions is higher in men, although women have more lesions. Moreover, some women report having noticed the onset after hormonal changes such as menarche, pregnancy, and oral contraceptives. It is important to notice that these lesions can be asymptomatic or manifest as pain and itch caused by oscillations in pressure or temperature, swinging moods and direct contact.[32] Macroscopically, they are characterised as firm, smooth papules, or nodules between 2 to 20 millimetres in diameter and light red to brown in colour. Under the microscope, they can be distinguished into three different histological types. Piloleiomyomas are the most frequent type, rising from hair follicles' piloerector muscles, usually located over the trunk, upper/lower extremities, and shoulders. Genital leiomyomas can originate from the nipple-areola

complex, dardoic smooth muscle tissue of vulva and scrotum. Angioleiomyomas are derived from the smooth muscle tissue in the tunica media of the blood vessels.[33, 34] These dermatologic abnormalities can be clustered or scattered, unnoticed or highly noticeable. As most of the clinical phenotypes are mild, patients do not seek dermatological assistance. These lesions are similar to dermatofibromas, sebaceous cysts, neurofibromas and intradermal nevi. That said, skin biopsy has a central role when it comes to diagnosis.[32, 34] Treatment options should be discussed with the patient. Due to the high risk of continuous growth, the only curative management is surgical removal with clear margins to reduce risk of recurrence. Mild cases can have a conservative treatment by avoiding causative agents that can elicit pain or itch, and cosmetics camouflage. Acceptable treatments in small lesions or locations where surgical excision cannot be performed are carbon dioxide laser ablation, cryotherapy or electrodessication.[28, 34] Pain in leiomyomas can be medically managed with nitroglycerin, phenoxybenzamine, nifedipine, and doxazosin.[34]

The cumulative risk for RCC has been reported to be around 15% but this number is still uncertain as there are cohorts with different incidences.[35] Classically, renal cell carcinoma on HLRCC has been associated with papillary type 2 RCC. The unique renal cell carcinoma histological and cytological characteristics in HLRCC made WHO classify this familiar predisposition syndrome associated renal cell carcinoma in a different category – Hereditary leiomyomatosis and renal cell carcinoma – associated renal cell carcinoma. Histologically, they are described as papillary-like tumours with nucleoli with perinucleolar clearing, large nuclei, and eosinophilic cytoplasm.[36] A recent research demonstrated an incidence of 12.4% in renal tumours.[29] However there were some limitations when it comes to histological classifications, as part of the data available was before 2016 WHO's classification. The mean age for diagnosis is around 41-44 years old, but 1-2% of patients have RCC before the second decade of life and a higher metastasis risk.[29, 35] Although classically associated with multifocal and bilateral tumours, different studies have demonstrated that this tumour is predominantly unilateral and solitary.[29]

Uterine leiomyomas usually manifest 6.8 years after cutaneous leiomyomas. Compared with the nonsyndromic presentation, uterine leiomyomas associated with HLRCC have a wider diameter and are numerous. Women report having gynaecological symptoms (menorrhagia, reduced fertility, and fibromas) around 20 years old, which requires myectomy or hysterectomy at an early age. Microscopy features are similar to the sporadic type, making the diagnosis more difficult.[29, 32]

There are no criteria available for whom should integrate genetic testing. Based on the clinical presentation, it is recommended that the patient with cutaneous piloleiomyomas should have skin biopsy for histological confirmation and at least one of the following: surgical treatment for uterine

leiomyoma before the age of 40, surgical treatment for papillary type 2 RCC before the age of 40 or a first-degree family member with these criteria. Renal cell carcinoma screening should be initiated at 8-10 years old with annual MRI. Due to the high risk of metastasis in small primary tumours, all identified tumours should be surgically removed with partial nephrectomy. When in doubt if partial nephrectomy is curative, radical nephrectomy should be performed.[25, 29, 35, 37]

Tuberous sclerosis complex

Tuberous sclerosis complex (TSC; Online Mendelian Inheritance in Man #191100 and #613254) is a well-known genetic disease, first identified more than 100 years ago.[38-40] Currently, it is characterised as an autosomal dominant disease, which can virtually affect any organ system. TCS's phenotype is variable, even within an affected family.[41] The most frequently affected organs are the brain, skin, eyes, heart, lungs, and kidneys. Syndromic features vary from mild skin manifestations to debilitating neurologic abnormalities. The neurological afflictions are epilepsy, cortical brain malformations, intellectual disability, autism spectrum disorder, behavioural abnormalities, and glial-neuronal hamartomas. The cardiac system can present with cardiac rhabdomyomas that usually regress around the third year of life. When it comes to ophthalmologic manifestations, retinal astrocytic hamartomas can affect almost 50% of patients, usually not altering visual acuity. Retinal pigmentation, colobomas, palpebral angiofibromas, and iris depigmentation are also possible. Pulmonary features can be caused by pulmonary lymphangioleiomyomatosis, which has a late onset, around the fourth decade of life and is more frequent in women. Renal and dermatological manifestations will be discussed below. [39, 40, 42-44]

This phakomatosis has an incidence of 1 in 6 000-10 000 and a prevalence not related with race or gender, reaching over 2 million people globally. [45]

The clinical presentation results from TSC1 (9q34) or TSC2 (16p13) gene mutations encoding hamartin and tuberin proteins, respectively.[42] In contrast with other syndromes, TSC has approximately 70% of spontaneous mutations.[46] Moreover, 15% of individuals with clinical TSC diagnosis and no mutation identified by conventional methods, have TSC1 or TSC2 mutations identified by next-generation-sequencing, with 50% being mosaic.[41] Hamartin and tuberin proteins negatively regulate the mammalian target of rapamycin (mTOR) which is responsible for cell growth and proliferation. These mutations rise the levels of GTPase Ras homolog enriched in brain (Rheb-GTP) and activate mTOR complex 1 (mTORC1) which results in disorganised cellular overgrowth. It is consensual that TSC1 and TSC2 mutations follow the classic Knudson two-hit hypothesis. Although loss of heterozygosity is usually found in kidney features, when it comes to cortical manifestations this is not always true. Research has shown that manifestations such as autism or

altered brain connectivity rise from a single allele mutation on TSC1 or TSC2 and many hypotheses have proposed the influence of TSC1 or TSC2 mutations in the activation of Akt kinase.[42]

Skin manifestations of tuberous sclerosis complex include hypomelanotic macules (90%), angiofibromas (75%), fibrous cephalic plaques (25%) and shagreen patches (50%) (fig. 2). Hypomelanotic macules are elongated with sharp edge figure, initially named ash leaf spots because of its appearance. Varying from 2 to 40 millimetres in size, they are considered one of the first manifestations of TSC. More than three lesions (≥ 5 millimetres) are needed to make this diagnosis possible, as less than three lesions are common in healthy children. Confetti lesions are a subtype of hypomelanotic macules, but they are considered as a separate diagnostic manifestation as they are smaller (1-2 millimetres), multiple and can be clustered. It is important to highlight that these lesions can appear in adulthood as a consequence of sunlight exposure which should be considered as a differential diagnosis. In individuals with fair skin, Wood's lamp is useful as a diagnostic tool. Angiofibromas are cutaneous hamartomas affecting the connective and vascular tissue localised in the malar area, nasolabial folds, and chin. Macroscopically they start as an erythematous macule and evolve to red-brown silky shiny papules. The onset of these skin features is around 2 to 5 years old, and they tend to increase in number with age. As they can be disfiguring, patients usually seek the dermatology help. If not correctly accessed, they can be mistaken by adenoma sebaceum. Fibromas can also appear in the nailfolds, described in literature as Koenen tumours, and emerge as red streaks which narrows proximally. The onset age is usually one decade after skin angiofibromas and are more common in women. Fibromas can also manifest in the oral mucosa appearing with a violaceous colour or indistinguishable from the mucosa. Another frequent manifestation is dental pitted enamel, seen in almost all patients with the diagnosis. Fibrous cephalic plaques are part of angiofibromas, and they appear as a small, yellow-brown firm plaque localised on the forehead, scalp, and face. Shagreen patches are also frequent, usually in childhood. Localised in lumbosacral area, they can be hypopigmented, hyperpigmented or normal in colour with an orange peel appearance.[47-49] Dermatological treatment in TSC is limited. Facial and ungual fibromas should be treated as early as possible with options such as shave excision, laser, cryosurgery, dermabrasion, and desiccation and curettage. [49]

Renal disease in tuberous sclerosis complex has a high mortality burden. Throughout their lives, renal angiomyolipomas, epithelial cysts, and less frequently renal cell carcinomas develop, conducting to nephrosparing surgery and a high risk of haemorrhage which leads to chronic kidney disease with renal replacement therapy or life-threatening events. Renal cell carcinoma affects approximately 2 to 4% of the individuals diagnosed with tuberous sclerosis complex. They are described as multiple and bilateral and research has shown that different RCC in the same individual

have different TSH1 or TSH2 second hit mutations, confirming that each tumour forms independently. The median age of onset is around 36 years old, but some cases have been reported in infants. Histologically, they have been identified as clear cell RCC, papillary RCC, chromophobe RCC or renal oncocytoma.[45]

The most recent diagnostic recommendations on TSC refer to the 2012 International Tuberous Sclerosis Complex Consensus Conference, summarised in table III. When compared with 1998 Consensus Conference Clinical Diagnostic Criteria, the identification of the mutation TSC1 or TSC2 makes the diagnosis of TSC. Therefore, individuals with family history of TSC who wish to be screened for the mutation while asymptomatic have with certainty the diagnosis of the disease, taking into consideration that a negative test does not exclude the disease.[49, 50]

Understanding the tumour genesis, allows target treatment of these lesions. That said, mTORC1 inhibitors are a possible option for non-dermatological features. Drugs approved are everolimus for renal angiomyolipomas and subependymal giant cell astrocytoma and sirolimus for lymphangioleiomyomatosis.[49, 50]

PTEN hamartoma tumour syndrome

Cowden syndrome-1, Bannayan-Riley-Ruvalcaba syndrome, Proteus syndrome, and Proteus-like syndrome are different clinical syndromes characterised by the mutation on the tumour suppressor gene phosphatase and tensin homolog (PTEN). [43, 51] PTEN's gene mutation was first identified in different sporadic carcinomas, being associated with Cowden syndrome only in 1997, and later with the remaining syndromes, composing PTEN hamartoma tumour syndrome (PHTS; Online Mendelian Inheritance in Man #158350).[52, 53] PHTS has a broad-spectrum phenotype which includes neurologic features (macrocephaly, autism spectrum disorder, development delay), non-malignant manifestations such as vascular malformations, skin features (palmoplantar keratosis, trichilemmoma, papillomatous, papule, lipoma, fibroma, penile freckling), mucosal lesions, gastrointestinal polyposis (mostly hamartomatous polyps at a young age, but also ganglioneuromas, adenomatous and inflammatory polyps), benign breast disease, and malignancies (breast, epithelial thyroid, endometrial and colorectal cancer, renal cell carcinoma, and melanoma). [53-55] Throughout the years, Cowden syndrome-1 and Bannavan-Riley-Rubalcaba syndromes patients, were identified in the same family and to date are considered the same disease.[43, 53] Consequently, the assumption that these syndromes have similar cancer risks was made. Although well-recognised, data available mostly refers to Cowden syndrome, from which extrapolations have been made. [43]

Recent research is not available on the epidemiology of PHTS. Thus, Cowden syndrome's 1999 prevalence is the most recent data and estimated on 1:200 000. [54, 56]

PTEN mutation is a mendelian autosomal dominant disease that occurs on chromosome 10q23 with almost complete penetrance. It is estimated that 10.7 to 47.6% occurs as de novo mutations. PTEN regulates PI3K/AKT/mTOR signalling pathway. PI3K is responsible for the phosphorylation of PIP2 to PIP3, which in place activates AKT, its deletion results in unregulated cellular growth. Nine exons' mutations have been identified, being exon 5 the most frequently affected.[54]

Skin features are generally associated. It is believed that almost all patients with Cowden syndrome and most patients with Bannayan-Riley-Ruvalcaba have dermatologic manifestations. Trichilemmomas are skin-coloured papules varying from 1 to 5 millimetres localised in the face (mostly eye, mouth, nose, forehead), neck, axillae, and hands.[55, 57] Macroscopically they can be indistinguishable from trichoepitheliomas, fibrofolliculomas, common facial wart, reason why the skin biopsy is mandatory to confirm the diagnosis. Moreover, they are a rare sporadic skin manifestation, constituting a hindrance to the diagnosis. Acral keratosis is also a common feature, most frequently localised in hands' palmar surface and feet' sole, although non acral areas have also been identified. To the naked eye they correspond to wart-like lesions that can be palpable. Other skin features associated with PHTS are lipomas and venous and arterial vascular anomalies. Sclerotic fibromas of the skin are uncommon in general population. Although literature demonstrated their association with clinical diagnosis of Cowden syndrome, it is not consensual its association with PHTS. Oral cavity is also affected in almost 80% of patients. They can be differentiated in mucocutaneous neuromas (hamartoma of the peripheral nerve sheath) and oral papillomas and are characterised as whitish to skin-coloured papules or nodules with 1-3 millimetres, which can occur individually or with a cobblestone pattern. Other findings are periodontitis, extensive dental caries, and xerostomia.[55] One of the most frequent manifestations is macular pigmentation of the glans penis, initially identified in Bannayan-Riley-Ruvalcaba syndrome. [55]

PTEN mutations are associated with increased lifetime risks of developing tumours, characterised by early-onset, bilaterality and multifocality. The most pronounced one is breast cancer (25-50%), only proved to be higher in women, with an onset age around 38-50 years, followed by thyroid (35%), kidney (34%), endometrial (28%), colon (9%) cancer, and melanoma (6%). It is not certain if colon cancer is originated from adenomatous or hamartomatous polyps.

Kidney cancer was only associated with PHTS in 2000. The onset age is around 40 years old, and studies have shown that papillary type I (54,5%) followed by papillary type II (18,2%), chromophobe

(18,2%) and clear cell carcinoma (9,1%) are the most frequently associated RCC histology. [56, 58] A plausible strategy is annual screening with MRI, followed by a nephrosparing surgery in cases where a mass greater than 3 centimetres is found. Due to limited research available, the screening onset age is still not established. [59]

The diagnostic criteria available on PTEN hamartoma tumour syndrome (table IV) is an evidence-based review, adapting Cowden syndrome U.S. National Comprehensive Cancer Network. Clinicians should pay attention to characteristics suggestive of this syndrome, in order to signalise a possible germline PTEN mutation. If mutation is identified, all members of this patient's family should be screened for the mutation, regarding the psychological influence of a positive gene test. [55]

BAP1 tumour predisposition syndrome

BRCA-1 associated protein-1 tumour predisposition syndrome (BAP1-TPDS; Online Mendelian Inheritance in Man #614327) was described for the first time in 2011, by the time three independent research groups associated BAP1 mutation with higher risk for hereditary carcinomas.[60-62] It is an autosomal dominant transmitted disease with an estimated penetrance around 85%.[63] To date, BAP1-TPDS is associated with uveal melanoma, malignant mesothelioma, cutaneous melanoma, and renal cell carcinoma. Cutaneous melanocytic manifestations are also connected.[62-64] Additionally, tumours such as basal cell carcinoma, breast cancer, meningioma, cholangiocarcinoma, non-small cell lung adenocarcinoma, neuroendocrine tumours, and thyroid cancer have been associated with this syndrome. [65]

BAP1 gene mutation is the causative gene for this syndrome. Located in the short arm of chromosome 3 (3p21), this deubiquitinating enzyme is responsible for cell cycle control, cellular differentiation, and DNA damage repair, by deubiquitylating and stabilising type 3 inositol-1,4,5-triphosphate receptor (IP3R3), which in place modulates calcium release from the endoplasmic reticulum, promoting apoptosis. [66]

BAP1-TPDS cutaneous presentation include cutaneous melanocytic manifestations that affects almost 90% of patients and are known as melanocytic BAP1-mutated atypical intradermal tumours (MBAITs), "BAPomas", atypical Spitz tumours (ASTs), Wiesner nevi, or nevoid melanoma-like melanocytic proliferations (NEMMPs). These lesions are characterised as dome-shaped papules or nodules, pink to brownish in colour, and measure 0.2-1.0 centimetres. The most common locations include the face, trunk, and members and they can vary from 2 to 50 lesions. On dermoscopy, it is observed a structureless central area with lateral focal pigment globules. Histologically, they are described as intradermal lesions with epithelioid melanocytes. These have been described as round vesicular nuclei and abundant amphophilic cytoplasm with a nodular or sheet-like growth pattern.

Research has shown that the typical onset age is around 31 years old. The early onset age compared with other tumours characteristic of this syndrome, provides a great opportunity for diagnosis and screening of BAP1-TPDS. That said, pathologists play a major role in the identification of this syndrome. [63, 67, 68] It has been argued MBAITs are a benign condition. First research reported that they could not progress to cutaneous melanoma. However, faint orange-red pigment, red papule morphology and halo formation have been described in MBAITs and in cutaneous melanoma with BAP1 germline mutation, rising the suspicion that they are a melanoma precursor lesion.[68] Cutaneous melanoma is another common skin feature of BAP1-TPDS, affecting around 18% of patients with BAP1 germline mutations, with an onset age earlier than general population and worse prognosis, although data is inconsistent. [63, 66]

Renal cell carcinoma was only described as a syndromic feature in 2013. [69] It is estimated that 10% of patients with this mutation will develop kidney cancer, although this number may be overestimated. Usually, the diagnosis occurs around 47 years old and has a worse prognosis.[63, 66] It is mostly associated with clear cell renal cell carcinoma (ccRCC), however, 2 cases of non ccRCC have been reported. [70]

Uveal melanoma is a well-described associated feature. Research has shown its early onset when compared with sporadic uveal melanoma and worse outcome. The same is not proved in malignant mesothelioma. Although onset age is prior to the general population, research has shown a better outcome.[63]

BAP1 mutations are seen in germline and sporadic tumours. [64] That said, genetic testing should be offered when there is evidence of carcinoma with BAP1 deletion and personal or family history of cancer. [71] When it comes to ccRCC, research suggest the same protocol as von Hippel-Lindau, performing abdominal US and computed tomography (CT) annually or MRI every 2 years, following the three centimetres rule for evaluation of renal masses. Full skin examination should be performed annually by a dermatologist starting at 20 years old and every 6 months after 30 years old. The examination should be completed with dermatoscopy, and milder changes on MBAITs-like lesions should be excised. [71]

Von Hippel-Lindau syndrome

Von Hippel-Lindau syndrome (VHLS; Online Mendelian Inheritance in Man #193300) is an autosomal inherited disease characterised by benign and malignant vascular tumours. Although the term von Hippel-Lindau syndrome was commonly used since 1970, it was described by von Hippel in 1911 and by Lindau 1926.[72, 73] The most common features now recognised are retinal and central nervous system hemangioblastomas, multifocal ccRCCs, renal cysts, pheochromocytoma,

pancreatic islet tumours and endolymphatic sac tumours. Classically, this disease has been classified in type 1 and type 2 based on the risk of developing pheochromocytoma. That said, type 1 is related with ccRCC and type 2 with pheochromocytoma. Then, type 2 is divided in 2A, characterised by hemangioblastoma and pheochromocytoma, type 2B characterised by ccRCC, hemangioblastoma and pheochromocytoma, and type 2C only pheochromocytoma.[73, 74]

Overall incidence is estimated in 1:36 000 which represents one of the most frequent inherited cancer predisposition syndrome.[74]

This disease is caused by the inherited mutation on von Hippel-Lindau (VHL) gene, a tumour suppressor gene located in chromosome 3 (3p25-26) which encodes VHL protein. The loss of heterozygosity results in the accumulation of HIF-1 and HIF-2 influencing the transcription and expression of tumorigenic factors, such as vascular endothelial growth factor (VEGF) and platelet derived growth factor.[74] Genotype-phenotype correlations have been made based on interfamilial phenotypes and classical classifications. It is important to highlight that around 20% are de novo mutations and this mutated gene has a penetrance around 95%.[25]

Although not widely acknowledged, less than 5% of patients with the diagnosis have cutaneous vascular malformations that occur mostly in the head and neck. Café-au-lait spots are also possible, believed to be caused by an overlap with neurofibromatosis. That said, besides from being infrequent and nonspecific, physicians should be aware to spot these lesions specially in families with history of VHLS.[75, 76]

Clear cell renal cell carcinoma is a common feature in VHLS. Type 1 and 2B have an incidence risk of approximately 70% and an onset age around 40 years old. Renal cysts in VHL seem to be linked with RCCs. In fact, renal cysts' epithelium histology shows foci of microscopic tumours. Vigilance is important to signalize malignant masses. Guidelines suggests annually MRI to identify lesions with more than 3 centimetres. Whenever they are found, due to the risk of metastasis, nephrosparing surgery should be performed.[77]

Hemangioblastomas in the central nervous system (CNS) are the most common manifestation affecting 60 to 80% of patients with von Hippel-Lindau. They are formed usually in cerebellum, spinal cord and brain stem and present with symptoms associated with mass effect compression. Retinal angiomas can affect almost half of the germline mutation carriers. Physicians should be aware of the high prevalence of pheochromocytomas, characteristic of type 2, diagnosed by the age of 40. Research has shown a lower malignancy risk when compared with sporadic pheochromocytoma. Other common manifestations are pancreatic cysts and tumours and endolymphatic sac tumours.[72]

MiTF-associated cancer syndrome

Microphthalmia-associated transcription factor (MiTF) associated cancer syndrome is an emerging syndrome with skin abnormalities. MiTF is involved in the regulation of HIF-1α pathway, which in place is responsible for renal tumorigenesis. It has been associated with melanoma and renal cell carcinoma. [78] There are no guidelines available, yet some research suggests referencing to genetic counselling if personal or familiar history of RCC or melanoma. [79]

Discussion

Hereditary renal cell carcinoma syndromes with dermatological manifestations, outlined in this systematic review, are caused by autosomal dominant germline mutations, followed by the inactivation of the second allele, as proposed in the Knudson's two-hit hypothesis. These syndromes have a broad-spectrum phenotype with landmarks such as: early cancer onset age, multiple tumours, rare histological features, and extracutaneous manifestations characteristic of each phenotype. The incidence of renal cell carcinoma and skin features vary from syndrome to syndrome. The skin is, in most cases, the first affected organ providing an excellent vehicle for diagnosis. All physicians should be aware of these skin manifestations as they are a hint to an inherited cancer predisposition syndrome. That said, signalising these patients providing early diagnosis and integration in screening and follow-up programs can increase their life span.

Although easily accessed, the identification of these skin manifestations remains a challenge. The same lesions can occur in different syndromes or in general population. Many examples rise from our investigation: acrochordons present in BHDS are also frequent in general population, or café-au-lait macules characteristic of VHLS are also a manifestation of other syndromes (neurofibromatosis type 1) and are common nonsyndromic features. Moreover, angiofibromas can happen in BHDS and TSC. Another limitation to the identification of these lesions and consequently these syndromes is the macroscopically appearance to syndromic and nonsyndromic features. An example extracted from our research are leiomyomas macroscopically similar to dermatofibromas, sebaceous cysts and intradermal nevi. In addition, trichilemmomas, characteristic of PTEN hamartoma tumour syndrome are macroscopically identical to fibrofolliculomas (present in BHDS) and common facial wart.

Our research was restricted because of limited original population-based studies and meta-analysis providing an accurate epidemiology added to the absence of diagnostic criteria limiting the inclusion of these patients on population-based studies and meta-analysis.

To conclude, these syndromes display the importance of a holistic and multidisciplinary approach to a patient. It is important to highlight that many patients do not directly seek the dermatologist help because their skin manifestations are mild, non-symptomatic, and are undervalued because of its family history. We suggest that whenever these skin features are found, articulation with dermatology should be conducted for evaluation, and skin biopsy should be performed, if considered necessary. The exceptional skin and kidney histological features, such as MBAITS and HOCT, places the importance of pathology in the identification of these syndromes.

This article emphasises the importance of awareness of these rare syndromes by all physicians. The limited knowledge among specialists involved in the management of these syndromic features such as urologists, dermatologists, oncologists, pathologists, results in the non-diagnosis of these syndromes. Consequently, the follow-up process is overlooked, and the necessary lifetime follow-up protocol is not performed. Furthermore, high-risk relatives are unobserved and guided vigilance to kidney and other related tumours is not accomplished.

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Tables

Table I: Hereditary renal cell carcinoma syndromes with dermatological manifestations

Syndrome	Gene (position)	Kidney Histology	Incidence of kidney tumour (%)	RCC diagnosis age (years old)	Skin features	Incidence of skin features (%)	Other phenotypic features
Birt-Hogg-Dubé syndrome	17p11.2 FLCN	HOCT and oncocytoma	34	48-51	Fibrofolliculomas Trichodiscomas Acrochordons	90	Pulmonary cysts Spontaneous pneumothorax
Hereditary leiomyomatosis and renal cell cancer	1q43 FH	Hereditary leiomyomatosis and renal cell carcinoma – associated renal cell carcinoma	15	41-44	Piloleiomyomas Genital leiomyomas Angioleiomyoma	78	Uterine leiomyomas
Tuberous sclerosis complex	9q34 TSC1 16p13 TSC2	ccRCC, papillary RCC, chromophobe RCC and renal oncocytoma	2-4	36	Hypomelanotic macules Skin angiofibromas Ungual fibromas Shagreen patch “Confetti” skin lesions Intraoral fibromas	>90	Renal angiomyolipomas Renal cysts Multiple retinal hamartomas Subependymal nodules Subependymal giant cell astrocytoma Cardiac rhabdomyoma Pulmonary lymphangioleiomyomatosis Pulmonary angiomyolipomas
PTEN hamartoma tumour syndrome	10q23 PTEN	Papillary type I, papillary type II, chromophobe, ccRCC	34	40	Multiple trichilemmomas Acral keratoses Mucocutaneous neuromas Oral papillomas Macular pigmentation of the glans penis Lipomatosis	Uncertain (highly prevalent)	Breast cancer Endometrial cancer Thyroid cancer Gastrointestinal hamartomas Lhermitte-Duclos disease Macrocephaly Autism spectrum disorder Colon cancer Esophageal glycogenic acanthosis Mental retardation
BAP1 tumour predisposition syndrome	3p21 BAP1	ccRCC	10	47	MBAITs Cutaneous melanoma	90	Uveal melanoma Malignant mesothelioma
Von Hippel-Lindau syndrome	3p25-26 VHL	ccRCC	70% (Type 1 and 2B)	40	Cutaneous vascular malformations Café-au-lait spots	<5	Hemangioblastoma (CNS and retinal) Pheochromocytoma Pancreatic cysts and tumours Endolymphatic sac tumours
MiFT-associated cancer syndrome	–	–	–		Melanoma	–	–

Table II Diagnostic criteria for Birt-Hogg-Dubé syndrome

One major or two minor criteria are necessary	
Major criteria	≥5 fibrofolliculomas/trichodiscomas (One must be confirmed histologically)
	Pathogenic FLCN germline mutation
Minor criteria	Multiple lung cysts: bilateral basally located lung cysts with no other apparent cause, with or without spontaneous primary pneumothorax
	Renal cancer: early onset (<50 years) or multifocal or bilateral renal cancer, or renal cancer of mixed chromophobe and oncocytic histology
	A first-degree relative with BHD

Adapted from *Birt-Hogg-Dubé Syndrome: A Review of Dermatological Manifestations and Other Symptoms*[15]

Table III Diagnostic criteria for Tuberous sclerosis complex

Definite diagnosis: Two major features or one major feature and ≥ two minor features Possible diagnosis: Either one major feature or ≥ two minor features	
Major features	Hipomelanotic macules (≥3, at least 5 mm diameter)
	Angiofibromas (≥3) or fibrous cephalic plaque
	Ungual fibromas (≥2)
	Shagreen patch
	Multiple retinal hamartomas
	Cortical displasias
	Subependymal nodules
	Subependymal giant cell astrocytoma
	Cardiac rhabdomyoma
	Lymphangioleiomyomatosis
	Angiomyolipomas (≥2)
Minor features	Confetti skin lesions
	Dental enamel pits (>3)
	Intraoral fibromas (>2)
	Retinal achromic patch
	Multiple renal cysts
	Non-renal hamartomas

Adapted from *Cutaneous manifestations of tuberous sclerosis complex and the paediatrician's role*[48]

Table IV Revised PTEN hamartoma tumour syndrome clinical diagnostic criteria

Operational diagnosis in an individual (either of the following):

1. Three or more major criteria but one must include macrocephaly, Lhermitte-Duclos disease, or gastrointestinal hamartomas; OR
2. Two major and three minor criteria.

Operational diagnosis in a family where one individual meets revised PTEN hamartoma tumour syndrome clinical diagnostic criteria or has a PTEN mutation:

1. Any two major criteria with or without minor criteria; OR
2. One major and two minor criteria; OR
3. Three minor criteria.

Major criteria	Breast cancer Endometrial cancer (epithelial) Thyroid cancer (follicular) Gastrointestinal hamartomas (including ganglioneuromas but excluding hyperplastic polyps; ≥3) Lhermitte-Duclos disease (adult) Macrocephaly (≥P97: 58 cm for females, 60 cm for males) Multiple mucocutaneous lesions (any of the following): Multiple trichilemmomas (≥3, at least one biopsy proven) Acral keratoses (≥3 palmoplantar keratotic pits and/or acral hyperkeratotic papules) Mucocutaneous neuromas (≥3) Oral papillomas (particularly on tongue and gingiva), multiple (≥3) OR biopsy proven OR dermatologist diagnosed
Minor criteria	Autism spectrum disorder Colon cancer Esophageal glycogenic acanthosis (≥3) Lipomas (≥3) Mental retardation (ie, IQ ≤ 75) Renal cell carcinoma Testicular lipomatosis Thyroid cancer (papillary or follicular variant of papillary) Thyroid structural lesions (eg, adenoma, multinodular goiter) Vascular anomalies (including multiple intracranial developmental venous anomalies)

Adapted from *Cowden syndrome and the PTEN hamartoma tumor syndrome: systematic review and revised diagnostic criteria*[55]

Figures

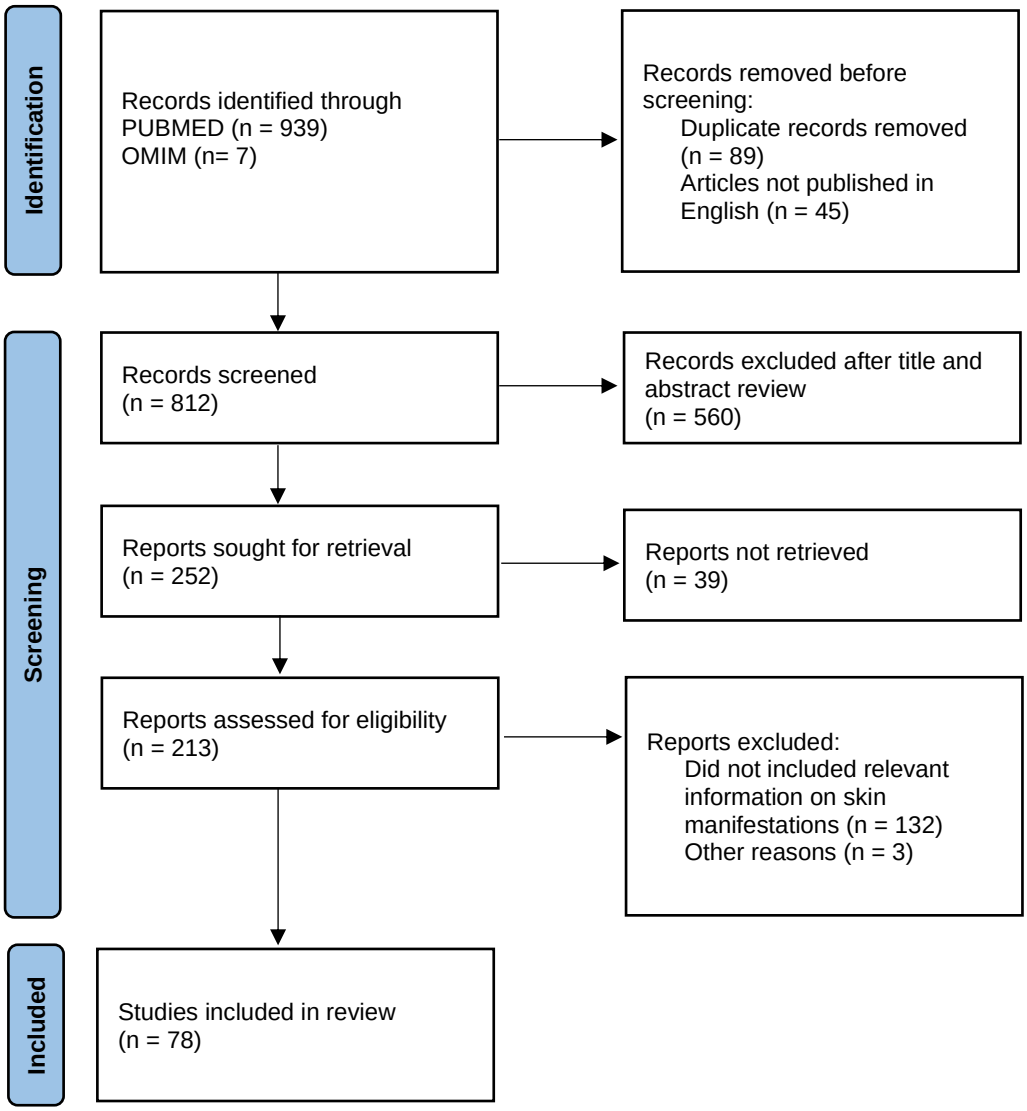

Figure 1: The PRISMA flow diagram outlining the search performed

Adapted from *The PRISMA 2020 statement: an updated guideline for reporting systematic reviews*.[10]

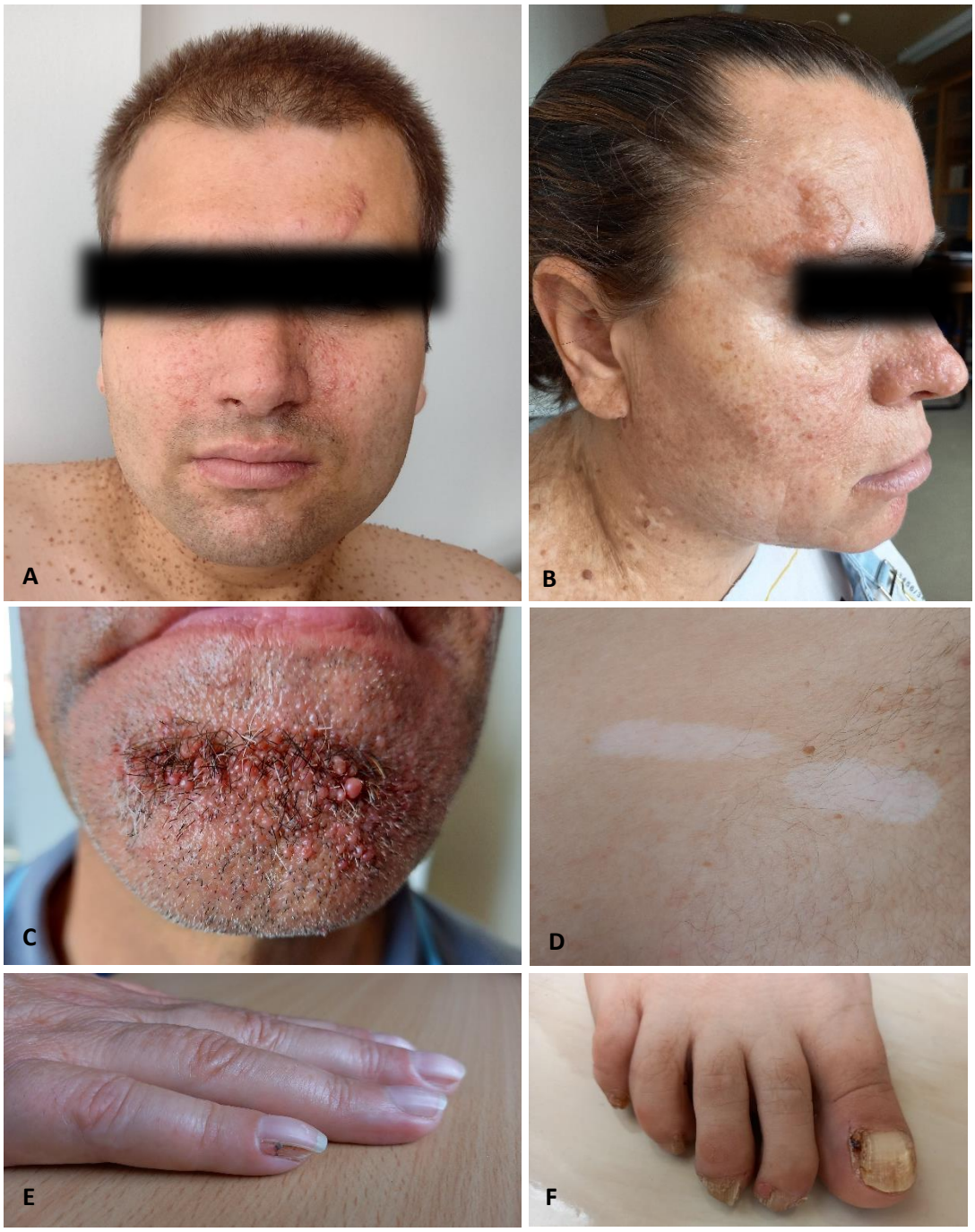

Figure 2: Dermatologic manifestations of Tuberous sclerosis complex

Red-brown papules observed in the malar area and nose (A-B) and chin (C) in three patients with TSC's diagnosis, suggestive of angiofibromas. Two skin-coloured, yellow firm plaques localised in the forehead were noticed, indicating fibrous cephalic plaques (A-B). Hypomelanotic macules, with ash leaf's appearance, were also present in the trunk of one of the patients (D). Red streaks emerging from the nailfold were present in the female patient, both in hand and feet, suggestive of Koenen tumours (E-F).