Be vigilant for skin manifestations of inherited cancer syndromes

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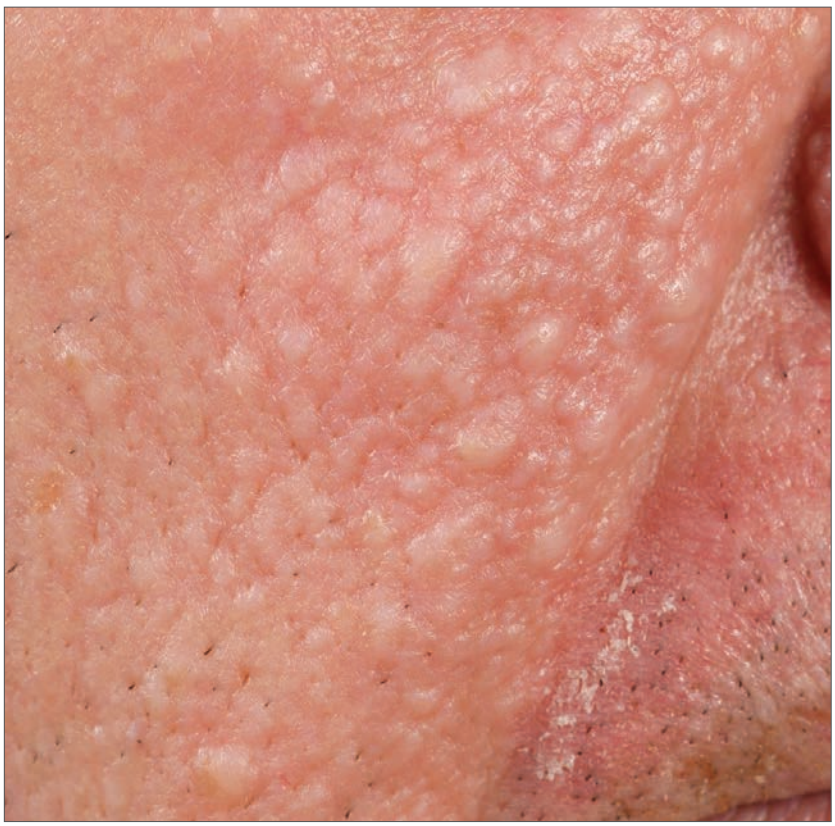

FIGURE 1
Fibrofolliculomas on the face of a middle-aged man belonging to a pedigree of Birt-Hogg-Dubé syndrome

How should diagnosis be confirmed?

What are the management approaches?

How should patients be monitored?

A CANCER SYNDROME IS A GENETIC DISORDER THAT PREDISPOSES THE AFFECTED INDIVIDUAL to the development of primary malignant tumours, often involving multiple organ systems, including the skin, and occurring at an earlier age than their sporadic equivalents.

More than 200 hereditary cancer susceptibility syndromes have been described and it is thought that they account for 5-10% of all cancers.[1]

Many familial cancer syndromes have dermatological manifestations (usually lesions, occasionally rashes), and frequently the cutaneous signs precede other systemic pathology. They demonstrate considerable variety, from the lentigines of Peutz-Jeghers syndrome, and the innocuous looking fibrofolliculomas of Birt-Hogg-Dubé syndrome, to the epidermoid cysts of Gardner syndrome.

They may be relatively easy to diagnose, such as the soft neurofibromas of neurofibromatosis and the painful leiomyomas of Reed's syndrome, but they are usually non-specific and often trivial in appearance, making their significance easy to overlook and clinical diagnosis challenging. As a result, histological examination is often required to differentiate lesions. They are usually benign and pathologically unrelated to the primary tumours, with the exception of the atypical moles of the dysplastic naevus syndrome, and may present simply as a cosmetic problem for the patient.

PATHOGENESIS OF CANCER SYNDROMES

Recent advances in molecular genetics have led to a greater understanding of the pathogenesis of cancer syndromes. Most are inherited in an autosomal dominant pattern, demonstrating complete penetrance (all carriers of the gene will develop the condition) before the age of 70. The mutated genes are often involved in aspects of cell cycle regulation, and include tumour suppressor genes, DNA repair genes and oncogenes.

For example, the colorectal tumours associated with Muir-Torre (Lynch) syndrome are characterised by their microsatellite instability (nucleotide repeats with high mutation rates) through the inheritance of a germline mutation in DNA mismatch repair mechanisms that are important for the correction of concordance errors in newly replicated DNA.[2] This biomolecular instability has also been observed in the sebaceous tumours associated with the syndrome, demonstrating a common pathogenesis.

Since mutations in the FLCN gene were identified as the genetic basis of Birt-Hogg-Dubé syndrome in 2002, the functions of the encoded protein folliculin, which is subsequently »

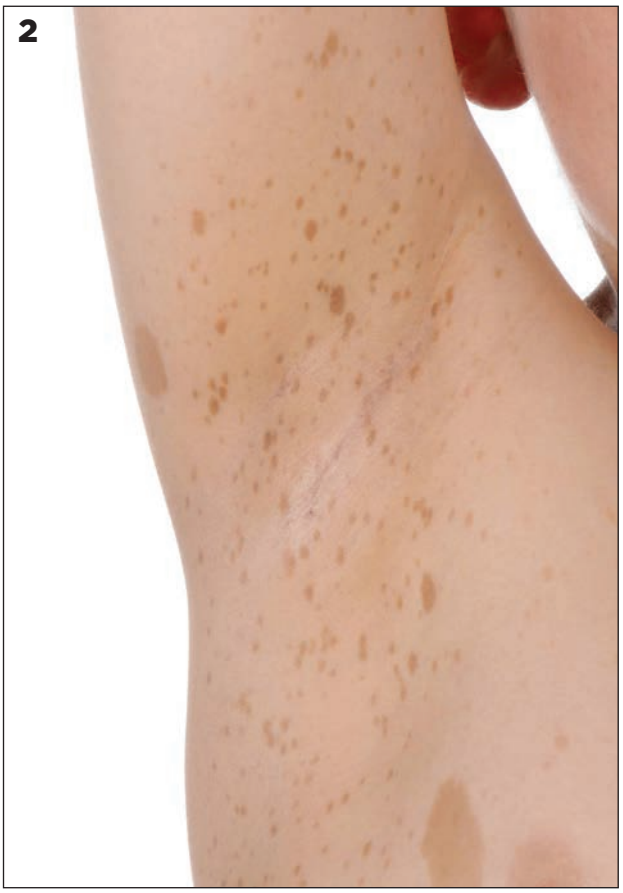

FIGURE 2
Café au lait patches and axillary freckling (Crowe's sign) in an adolescent with neurofibromatosis type 1

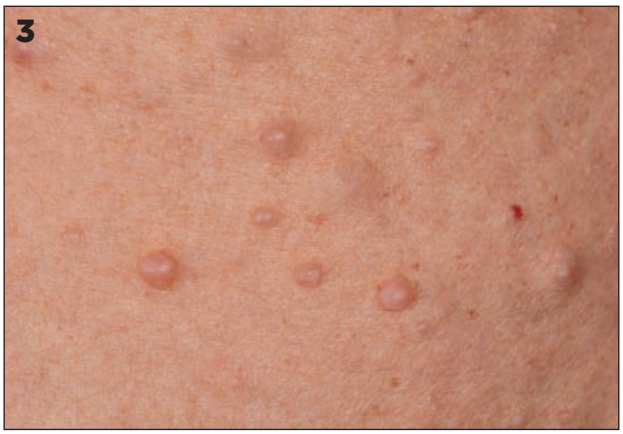

FIGURE 3
A cluster of soft neurofibromas in an adult with neurofibromatosis type 1

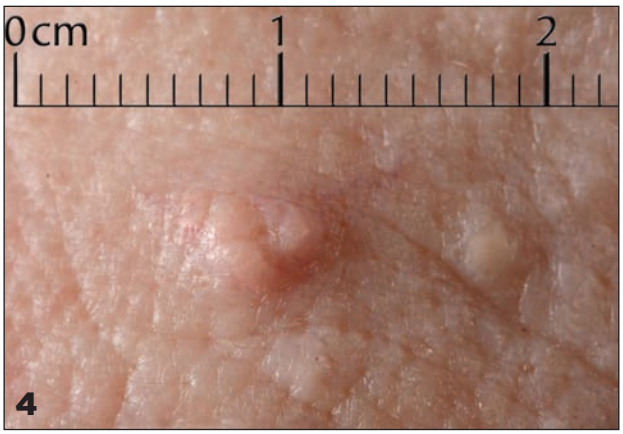

FIGURE 4
A sebaceous adenoma on the forehead of a middle-aged woman, initially thought to be a basal cell carcinoma. In this instance, the expression of mismatch repair proteins was intact, thus excluding Muir-Torre syndrome

inactivated, are still being studied.[3] However, it is considered to be a tumour suppressor protein.

CUTANEOUS MANIFESTATIONS OF CANCER SYNDROMES

The list of inherited cancer syndromes continues to grow and the spectrum of associated cutaneous manifestations is broad, see table 1, opposite.

The majority of cancer syndromes with skin signs are autosomal dominant. Autosomal recessive cancer syndromes with dermatological features include ataxia telangiectasia, Bloom syndrome, Werner syndrome, xeroderma pigmentosum, and Rothmund-Thomson syndrome.

Some examples of cancer syndromes serve to illustrate the variety of skin involvement. For instance, Birt-Hogg-Dubé syndrome is characterised by multiple fibrofolliculomas (benign tumours of the hair follicle). These are dome-shaped, flesh coloured, smooth papules on the face and neck that can be easily mistaken for comedones, see figure 1, p23. Renal tumours develop in 12-34% of patients, and there is an increased risk of pulmonary cysts (84% of affected individuals), predisposing to spontaneous pneumothorax, which is often a diagnostic clue in a patient's family history, see box 1, p27.[3]

Neurofibromatosis type I (von Recklinghausen's disease) is a relatively common condition, which usually presents with café au lait patches and axillary freckling (Crowe's sign), see figure 2, above. The cutaneous neurofibromas that subsequently appear are soft and flesh coloured, and can be confused with simple melanocytic naevi especially when present in small numbers, see figure 3, above. Individuals affected with neurofibromatosis are at risk of malignant peripheral nerve sheath tumours and juvenile myelomonocytic leukaemia, as well as optic glioma and phaeochromocytoma.

Muir-Torre syndrome is the association of a sebaceous gland tumour (an adenoma, sebaceoma or carcinoma) with internal malignancy. These tumours are usually small nondescript papules on the face, scalp and eyelids, often misdiagnosed on the basis of the clinical features as basal cell carcinomas, see figure 4, above. Sebaceous tumours are rare and if discovered should raise the suspicion of Muir-Torre syndrome. The syndrome shares the same genetic pathogenesis as Lynch syndrome (hereditary non-polyposis colorectal cancer syndrome), and is associated with colorectal, endometrial and ovarian cancer.[2]

Another cancer syndrome with significant morbidity and mortality is Gardner syndrome, a subset of familial adenomatous polyposis (multiple colonic polyps which have a very high risk of malignant transformation). In addition to colorectal cancer, Gardner syndrome is associated with malignancies occurring in other organs, albeit much less frequently, including the small intestine, stomach, pancreas, liver, thyroid and central nervous system. More than 50% of individuals with Gardner syndrome develop epidermoid cysts, and it is their number, distribution (often on the face, scalp and extremities rather than the trunk), and their presentation at a young age (during puberty) that indicates that they might be a marker for internal malignancy.[4]

A number of cancer syndromes exhibit an increased risk of developing malignant skin lesions. For instance, Gorlin syndrome (nevoid basal cell carcinoma syndrome) typically results in the development of multiple basal cell carcinomas, usually within the first

Table 1

Autosomal dominant cancer syndromes

Cancer syndrome	Cutaneous manifestations	Associated features	Genetic defect
Birt-Hogg-Dubé syndrome	Fibrofolliculomas, trichodiscomas, acrochordons (skin tags), papules on buccal mucosa, collagenomas, facial angiofibroma	Renal tumours, including renal cell carcinomas and unusual histological types (can be bilateral), pulmonary cysts, pneumothorax, melanoma, parathyroid adenoma	Mutation in FLCN gene on Ch17p11.2 which codes for protein folliculin (tumour suppressor gene)
Muir-Torre syndrome (variant of hereditary nonpolyposis colorectal cancer syndrome)	Sebaceous adenoma, sebaceoma, sebaceous carcinoma, keratoacanthoma, squamous cell carcinoma, follicular cysts	Colorectal cancer, other gastrointestinal cancer, genitourinary cancer	Microsatellite instability leading to loss of MLH1 and MSH2 (DNA mismatch repair proteins)
Neurofibromatosis 1	Cutaneous and subcutaneous neurofibromas, café au lait spots, axillary freckling	Lisch nodules, scoliosis, plexiform neurofibromas, optic gliomas, phaeochromocytomas, gastrointestinal tumours, malignant peripheral nerve sheath tumours, brain tumours (meningiomas), childhood leukaemia	Mutation in NF1 gene on Ch17q11.2 which codes for neurofibromin (tumour suppressor)
Cowden syndrome (multiple hamartoma syndrome)	Trichilemmomas (well defined smooth papule/verrucoid growth), mucosal papillomatosis, acral keratosis, lipomas, haemangiomas	Breast cancer, fibrocystic breast disease, follicular thyroid cancer, endometrial cancer, uterine leiomyomas, gastrointestinal polyps	Germline intragenic mutations in PTEN gene on chromosome 10q23
Carney complex	Lentigines, blue naevus	Cardiac myxomas, testicular tumours, pancreatic cancer	Mutations in PRKAR1A gene (tumour suppressor gene)
Peutz-Jeghers syndrome	Peri-oral and oral lentigines	Hamartomatous gastrointestinal polyps, gastrointestinal cancer, pancreatic cancer	Mutation in STK11 (tumour suppressor gene)
Tuberous sclerosis	Periungual fibromas, facial angiofibromas, Shagreen patch, ash leaf macules	Renal angiomyolipomas, subependymal nodules, giant cell astrocytomas, cardiac rhabdomyomas	Mutation in TSC1 or 2 which produce hamartin and tuberin (tumour suppressor proteins)
Dysplastic naevus syndrome	Melanocytic naevi, melanoma	Melanoma, pancreatic cancer	Mutations in CDKN2A gene on chromosome 9
Howel-Evans syndrome	Palmoplantar hyperkeratosis, leukoplakia	Oesophageal cancer	Mutation in RHBDF2 on Ch17
Gorlin syndrome (nevoid basal cell carcinoma syndrome)	Basal cell carcinomas, palmar/plantar pits	Odontogenic keratocysts, childhood medulloblastomas, ovarian fibroma, cardiac fibroma, calcification of cerebral falx	Mutation in tumour suppressor gene PTCH1 on Ch9q22.3
Reed's syndrome (hereditary leiomyomatosis and renal cell cancer syndrome)	Cutaneous leiomyomas	Renal cell carcinoma, uterine leiomyosarcoma, fibroids, bladder cancer, breast cancer	Mutation in fumarate hydratase gene, which leads to accumulation of fumarate
Gardner syndrome (variant of familial adenomatous polyposis)	Epidermoid cysts, lipomas, leiomyomas, fibromas, neurofibromas	Colonic adenomatous polyps, colorectal cancer, osteomas (especially mandible), desmoid tumours, papillary thyroid cancer, hepatoblastoma, craniopharyngioma	Germline mutations in the adenomatous polyposis coli (APC) gene

key points

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More than 200 hereditary cancer susceptibility syndromes have been described, and it is thought that they account for 5-10% of all cancers. Many have dermatological manifestations (usually lesions, occasionally rashes) which frequently precede other systemic pathology. They demonstrate considerable variety, from the lentigines of Peutz-Jeghers syndrome, and the innocuous looking fibrofolliculomas of Birt-Hogg-Dubé syndrome, to the epidermoid cysts of Gardner syndrome.

Dermatological signs are usually non-specific and often trivial in appearance, making their significance easy to overlook and a clinical diagnosis challenging. Histological examination is often required to differentiate lesions. They are usually benign and pathologically unrelated to the primary tumours, with the exception of the atypical moles of the dysplastic naevus syndrome, and may present simply as a cosmetic problem for the patient. However, a number of cancer syndromes exhibit an increased risk of developing malignant skin lesions. For instance, Gorlin syndrome (nevoid basal cell carcinoma syndrome) which typically results in the development of multiple basal cell carcinomas, within the first few decades of life.

The majority of cancer syndromes with skin signs are inherited in an autosomal dominant pattern demonstrating complete penetrance before the age of 70. Autosomal recessive cancer syndromes with dermatological features are less common but include ataxia telangiectasia, Bloom syndrome, Werner syndrome, xeroderma pigmentosum, and Rothmund-Thomson syndrome.

Once a cancer syndrome has been diagnosed, the cornerstone of management is frequent surveillance for the early detection and treatment of malignancy. Genetic testing and counselling should be offered to family members. With advances in the identification of the specific gene mutations involved in individual cancer syndromes, the opportunity for novel, tailored, gene specific treatment is widening.

For some of the cancer syndromes, the skin lesions can be extensive and unsightly and may lead to low self-confidence, social stigma and isolation. The psychological implications of positive genetic (predisposition) tests include coping with the unpredictability of developing a malignancy, and concern about the future effect on offspring.

few decades of life. Close inspection usually reveals palmar and plantar pits, caused by defects in the stratum corneum, in about 85% of patients over the age of 20. A characteristic phenotype, with macrocephaly, frontal bossing and skeletal abnormalities, including odontogenic keratocysts (benign but often aggressive developmental cysts arising in the mandible or maxilla), is evident in 60% of patients with Gorlin syndrome, and there is a high risk of affected individuals developing multiple neoplasms, such as childhood medulloblastomas, meningiomas, and ovarian and cardiac fibromas.[5]

MANAGEMENT OF CANCER SYNDROMES

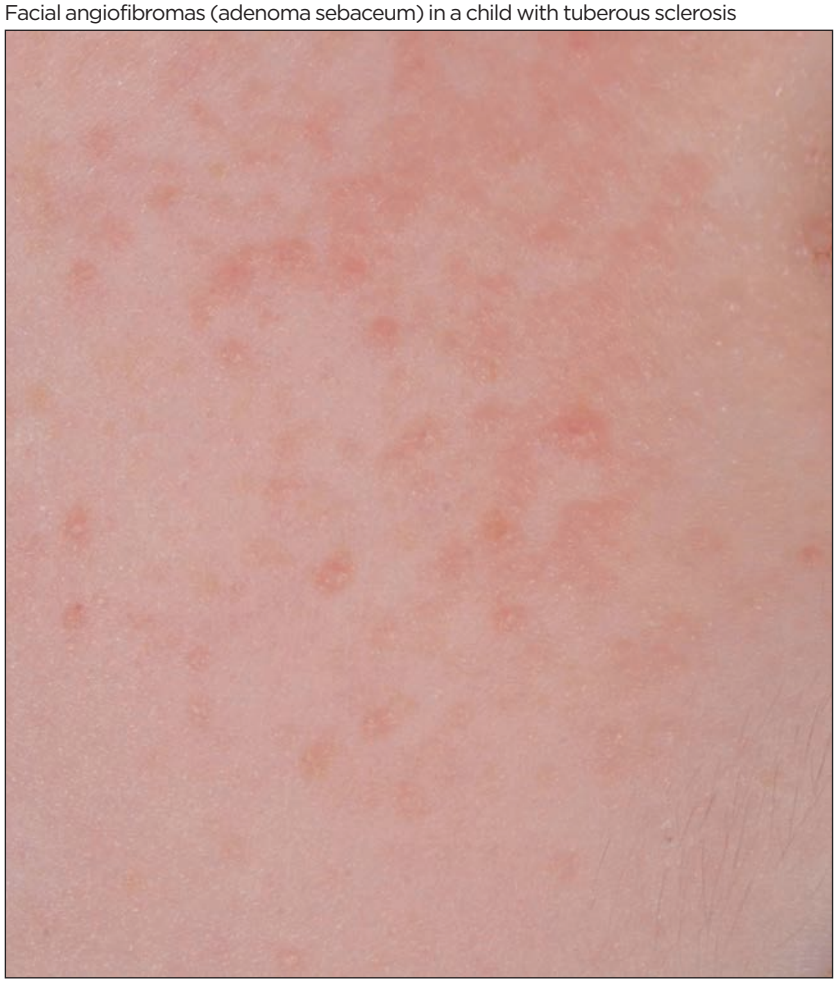
Once a cancer syndrome has been successfully diagnosed, the cornerstone of management is frequent surveillance for the early detection and treatment of malignancy, under specialist guidance. Genetic counselling and subsequent genetic testing should be offered to family members, and is now available for many of the mutations described.

With advances in the identification of the specific gene mutations involved in individual cancer syndromes, the opportunity for novel, tailored, gene specific treatment widens.

Currently the therapeutic options are limited but with promising results from BRAF inhibitors (for example vemurafenib and dabrafenib) and MEK inhibitors (for example trametinib and cobimetinib) in metastatic malignant melanoma,[6] the potential for targeted therapies is growing. Already in Gorlin syndrome, vismodegib (an inhibitor of hedgehog signalling pathway) has been used to reduce basal cell carcinoma burden.[7]

The demonstration of overactivation of mTOR signalling in animal models of Birt-Hogg-Dubé syndrome has lead to trials of rapamycin (an mTOR inhibitor), already used as an effective treatment for angiofibromas in tuberous sclerosis,[3] see figure 5, below. However, targeted

FIGURE 5
Facial angiofibromas (adenoma sebaceum) in a child with tuberous sclerosis



therapies are currently not available for the prevention of malignancies.

With regard to the treatment of the skin lesions themselves, this depends on the diagnosis and patient preference. In patients with Gorlin syndrome and dysplastic naevus syndrome, where the skin lesions are potentially malignant, treatment is the same as for sporadic skin cancers; surgical excision and emphasis on sun protection. For the benign skin lesions associated with internal malignancies, patients may request removal of asymptomatic lesions for cosmetic reasons. Potential treatments include electrocautery of fibrofolliculomas, laser treatment of facial angiofibromas, and oral retinoids (acitretin) for the cutaneous manifestations of Cowden syndrome.

Patients with cutaneous manifestations of cancer syndromes not only suffer from the potential implications but also from a psychosocial burden. For some of the cancer syndromes, the skin lesions can be extensive and unsightly often leading to low self-confidence, social stigma and risk of isolation.

Furthermore, the psychological implications of positive genetic (predisposition) tests include coping with the unpredictability of developing a malignancy, and concern about the future effect on offspring.

CONCLUSION

There is a maxim that the skin acts as a window into the inner workings of the body, and the inherited cancer syndromes are a group of conditions that may provide an opportunity for the astute clinician to diagnose, from cutaneous signs alone, an underlying genetically based tendency to malignancy. The significance of such signs may not be obvious given their often non-specific and apparently trivial nature, see box 1, above.

It is prudent to undertake a skin biopsy for histological evaluation before considering cosmetic surgery with destructive techniques on lesions that lack a diagnosis.

The inherited cancer syndromes are an example of how clinicians can learn from the characteristics of Sherlock Holmes: to observe keenly, to pay particular attention to detail, and to keep an open mind to seemingly irrelevant and inconsequential complaints, enshrined in the concept of 'Sherlockian dermatology'.[8]

Box 1

Case report

A 48-year-old woman presented with numerous small flesh coloured papules on her face and neck, see figure 6, below. Previously, these had been treated without a histological diagnosis, by curettage and laser therapy, with only modest improvement.

A small skin biopsy of a lesion on her neck was taken and histological examination showed it to be a fibrofolliculoma. As multiple fibrofolliculomas are a feature of Birt-Hogg-Dubé syndrome, an autosomal dominant cancer syndrome, her family history was explored. This revealed a number of her relatives to have had similar facial lesions, some to have had spontaneous pneumothorax and one to have had a renal tumour, thus confirming the diagnosis of Birt-Hogg-Dubé syndrome.

Further investigation of this patient excluded pulmonary cysts but confirmed that she had a renal carcinoma. Progressive deterioration of her renal function proved fatal.

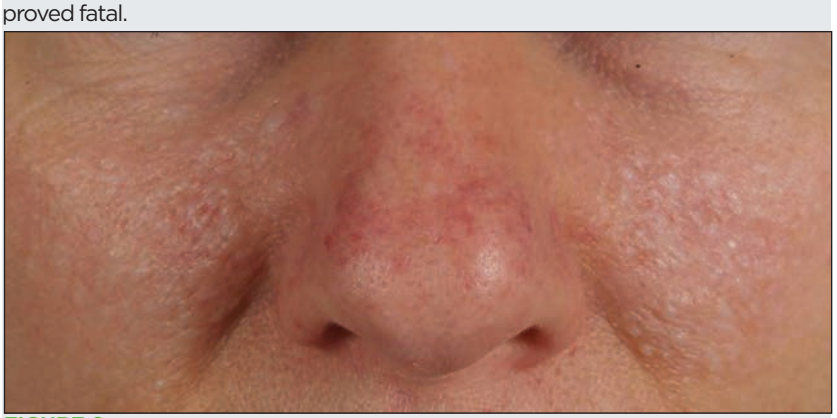


FIGURE 6
Facial fibrofolliculomas in a woman subsequently diagnosed with Birt-Hogg-Dubé syndrome

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Useful information

Macmillan Cancer Support
www.macmillan.org.uk/information-and-support/diagnosing/causes-and-risk-factors/genetic-testing-and-counselling

National Cancer Institute
Fact sheet on genetic testing for hereditary cancer syndromes
www.cancer.gov/about-cancer/causes-prevention/genetics/genetic-testing-fact-sheet

The Neuro Foundation
www.nfauk.org

Gorlin Syndrome Group
www.gorlingroup.org

BHD Foundation
Information and advice on Birt-Hogg-Dubé syndrome
www.bhdsyndrome.org

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