More Than Just Skin Deep: Faciocutaneous Clues to Genetic Syndromes with Malignancies

ZHU SHEN,^a JODI D. HOFFMAN,^b FEI HAO,^a ERIC PIER^c

^aDepartment of Dermatology, Southwest Hospital, Third Military Medical University, Chongqing, China;

^bDivision of Genetics, Floating Hospital for Children at Tufts Medical Center, Boston, Massachusetts, USA;

^cTufts Medical Center, Tufts University School of Medicine, Boston, Massachusetts, USA

Key Words. Faciocutaneous clue • Genetic syndrome • Malignancy • Neoplasm

Disclosures: The authors indicated no financial relationships.

ABSTRACT

Genetic syndromes with dermatologic findings and multisystemic involvement (e.g., visceral cancer predisposition) are underrecognized. Patients may have incomplete penetrance and variable expressivity; some patients may solely exhibit subtle skin signs, which create a diagnostic challenge for physicians. Interdisciplinary diagnostic knowledge is required for the early diagnosis and monitoring of patients with these syndromes. Cutaneous changes in the face—one of the most highly exposed areas—can be easily noticed by patients themselves, their families and friends, and physicians; these changes may serve as early indicators of genetic syndromes with malignancies. In this article, we present examples of genetic syndromes with malignancies for which a thorough faciocutaneous examination is helpful in establishing a diagnosis. These examples include lentiginosis-related syndromes (e.g., Peutz-Jeghers syndrome, Carney complex),

photosensitivity-related syndromes (Bloom syndrome, Rothmund-Thomson syndrome), and hamartoma-related syndromes (Cowden syndrome, multiple endocrine neoplasia syndrome, tuberous sclerosis complex, Gardner syndrome, Muir-Torre syndrome). The characteristics of these faciocutaneous clues are summarized and discussed. Objective evaluation of these faciocutaneous clues in combination with other clinical information (e.g., family history, histopathological findings, combination with other concomitant faciocutaneous lesions) is emphasized to narrow the diagnosis. The list of genetic syndromes with faciocutaneous manifestations is still expanding. Increased awareness of faciocutaneous markers can alert physicians to underlying syndromes and malignancies, render earlier screening and detection of associated medical issues, and allow for genetic counseling of family members. *The Oncologist* 2012;17:930–936

INTRODUCTION

Genetic syndromes with dermatologic findings and multisystemic involvement, including visceral cancer predisposition, are underrecognized. These syndromes often have incomplete penetrance and variable expressivity; patients may solely exhibit subtle skin signs, creating a diagnostic challenge to physicians. Interdisciplinary diagnostic knowledge is required for early diagnosis and monitoring of the patients with these syndromes. Cutaneous changes in the face—one of the most highly exposed areas—can be easily noticed by patients themselves, their families/friends, and physicians; these changes may serve as early indicators to genetic syndromes with ma-

lignancies. Thus, an awareness of the faciocutaneous hallmarks of genetic disorders is valuable to physicians.

Increased awareness of faciocutaneous markers can guide physicians in the diagnosis of multisystem genetic disorders, render earlier screening and detection of associated medical issues, and allow for genetic counseling of family members. In this article, we present examples of genetic syndromes with malignancies for which a thorough faciocutaneous examination is helpful in establishing a diagnosis. These examples include lentiginosis-related syndromes (e.g., Peutz-Jeghers syndrome, Carney complex), photosensitivity-related syndromes (Bloom syndrome, Rothmund-Thomson syndrome),

Correspondence: Zhu Shen, M.D., Ph.D., Department of Dermatology, Southwest Hospital, Third Military Medical University, 30 Gaotanyan Main Street, Shapingba District, Chongqing 400038, China. Telephone: 86-23-68767593; Fax: 86-23-68767593; e-mail: zhushencq@gmail.com Received January 21, 2012; accepted for publication May 8, 2012; first published online in *The Oncologist Express* on June 15, 2012. ©AlphaMed Press 1083-7159/2012/\$20.00/0 <http://dx.doi.org/10.1634/theoncologist.2012-0033>

Figure 1. General view of the full distribution of the lesions and the schematic section.

and hamartoma-related syndromes (Cowden syndrome, multiple endocrine neoplasia [MEN] syndrome, tuberous sclerosis complex, Gardner syndrome, Muir-Torre syndrome).

LENTIGINOSIS-RELATED SYNDROMES

Lentiginos are hamartomatous melanocytic proliferation lesions with increased hyperpigmentation in the basal layer of

epidermis. Morphologically, lentiginos are usually small (<5 mm), flat, sharply circumscribed, brown-to-black macules (Fig. 1A, 1B). They look like freckles (ephelides), but histologically freckles are due to an increased disposition of melanin in keratinocytes surrounding a normal number of melanocytes [1]. The pathogenesis of lentiginos is independent from sun exposure; they do not intensify and fade with sunlight

exposure as freckles do, but ultraviolet protection is indicated because of risk of malignant transformation. In addition, in contrast to age-related skin lesions, syndrome-related lentiginos typically manifest in prepubescence and fade in adulthood. Two syndromes in which faciocutaneous lentiginos are the indicator to the hiding syndromes with malignancies are Peutz-Jeghers syndrome and Carney complex.

Peutz-Jeghers syndrome, also called hamartomatous intestinal polyps-and-spots syndrome, is characterized by multiple gastrointestinal hamartomatous polyps and distinct melanocytic macules (lentiginos) dotting the lips, the mucosa of the mouth and anus, and distal extremities or diffusely over the body. (Figs. 1A, 2A) [2]. Patients with the syndrome have an increased risk of developing carcinomas, including gastrointestinal cancers and breast cancer (females) [3]. The lip lentiginos are the first sign on the face; they appear starting in infancy and can be identified at birth by experienced physicians. Lentiginos in Peutz-Jeghers syndrome appear throughout childhood and fade in adulthood.

Faciocutaneous lentiginos are also the most common facial lesions in Carney complex, which is a triad of spotty skin pigmentation, myxomas, and endocrine abnormalities with a predisposition to pituitary tumors [1, 4]. Faciocutaneous lentiginosis ranges from subtle single lesions to intense dense areas; lentiginos are typically found surrounding the vermilion border of the lips, on the nasal bridge, and on the conjunctiva (Figs. 1B, 2B). Cutaneous myxoma—abnormal growth of relatively undifferentiated tissue—is a complementary indicator to faciocutaneous lentiginosis in Carney complex. It is usually <1 cm in diameter, asymptomatic, and located on the eyelids and ears, appearing flesh colored or blue (Fig. 2B). Most patients with Carney complex and a life-threatening cardiac myxoma (intracardiac obstruction, stroke, and even myocardial infarction) initially present with cutaneous myxoma in early life [5].

PHOTOSENSITIVITY-RELATED SYNDROMES

Photosensitivity is defined as an abnormal response of the skin to ultraviolet radiation. Photosensitive lesions related to genetic syndromes present as persistent and pruritic papular, nodular, or erythematous eruptions (spidery rash), caused by dilated blood vessels. These lesions often occur on light-exposed areas, but occasionally occur on non-sun-exposed areas. Scarring, punctate atrophy, and variegation caused by hyperpigmentation and hypopigmentation of the skin are often observed after years of this recurrent rash. Photosensitivity may be due to medications, defective DNA repair (e.g., Bloom syndrome, Rothmund-Thomson syndrome, Xeroderma pigmentosum), or an unknown etiology.

Bloom syndrome (congenital telangiectatic erythema) is characterized by telangiectases and photosensitivity, growth deficiency, hypogonadism, variable degrees of immunodeficiency, lung disease, and increased susceptibility to a broad spectrum of neoplasias, including leukemias, lymphomas, and neuroblastoma [6]. Telangiectatic erythema on sun-exposed areas is developed as early as infancy, sometimes with blistering (Figs. 1C, 2C). This facial rash often forms as butterfly-

shaped reddened skin on the cheeks. Rothmund-Thomson syndrome (RTS; poikiloderma atrophicum and cataract) is characterized by chromosome fragility, developmental delay, dysmorphic features, and predisposition to cancers [7]. Two clinical subtypes of RTS have been defined. Patients with RTSII have increased risks of osteosarcoma at a younger age and skin cancer later in life [8]. The diagnostic hallmark of erythematous/edematous skin plaques often develops during the first year of life. They usually occur first on the cheeks, followed by the extremities and the buttocks, sparing the chest, abdomen, and back (Figs. 1D, 2D). Sparse eyelashes, eyebrows, and scalp hair as well as premature graying may also be observed (Table 1).

HAMARTOMA-RELATED SYNDROMES

A hamartoma is a disorganized mixture of tissue elements normally found in an organized fashion. They are often characterized by the appearance of larger papules or masses and can occur throughout the body, including the chin, face, heart, lungs, and kidneys. Hamartomas are generally benign, asymptomatic, and rarely invade, but sometimes obstruct adjacent organs. Hamartoma-related syndromes represent a large family of genetic syndromes. The faciocutaneous manifestations of hamartoma are diverse and prone to be neglected in clinical practice. Here we give more examples of faciocutaneous hamartomas (e.g., follicular hamartomas, angiofibromas, neuroomas, epidermoid cysts, sebaceous gland neoplasms, and keratoacanthomas) to comprehensively characterize their facial diagnostic clues.

Faciocutaneous hamartomas are found in nearly 100% of patients with Cowden syndrome (multiple hamartoma syndrome). Cowden syndrome is characterized by macrocephaly, benign facial hamartomatous overgrowths, and increased risks for thyroid, breast, and endometrial cancers with a female predominance (6:1) [9]. Women with Cowden syndrome have as high as a 25%–50% lifetime risk of developing breast cancer, with a generally younger diagnosis age than sporadic cases of breast cancer [10]. Faciocutaneous hamartomas in Cowden syndrome are generally developed by approximately 20 years of age and present before internal malignancies, allowing early recognition of the syndrome. They often present as 1- to 4-mm flesh-colored flat-topped or verrucoid papules; pathologically, they represent follicular hamartoma (proliferation of hair follicles). They are distributed mainly around the mouth, nose, and ears. Oral hamartomas often coalesce into a cobblestone appearance, especially on the tongue (scrotal tongue; Figs. 1E, 2E) [11].

Multiple facial angiofibromas are the most common and diagnostic skin abnormality for most patients with tuberous sclerosis complex (TSC) and MEN type 1 (Wermer syndrome) [12, 13]. TSC is characterized pathologically by the presence of hamartomas of the brain, skin, kidneys, heart, eyes, and lungs. Kidney angiomyolipomas, pulmonary lymphangiomyomatosis, and cardiac rhabdomyoma are the most common causes of mortality in TSC [14, 15]. Patients with MEN1 commonly have hyperparathyroidism, endocrine gastroenteropancreatic tract adenomas, and pituitary

Figure 2. Faciocutaneous markers of some genetic internal syndromes. (A): Peutz-Jeghers syndrome. (B): Carney complex. Reprinted from Rothacker D, Kerber C. Carney complex. Clinical, pathological and genetic features in two generations of a family. *Pathologie* 2008;29:294–300, with permission from Springer Science and Business Media. (C): Bloom syndrome. Reprinted from Balci S, Aktas D. Mucinous carcinoma of the colon in a 16-year-old Turkish boy with Bloom syndrome: cytogenetic, histopathologic, TP53 gene and protein expression studies. *Cancer Genet Cytogenet* 1999;111:45–48, with permission from Elsevier. (D): Rothmund-Thomson syndrome. (E): Cowden syndrome. Reprinted from Kovich O, Cohen D. Cowden's syndrome. *Dermatol Online J* 2004;10:3 and Oliveira MA, Medina JB, Xavier FC, Magalhães M, Ortega KL. Cowden syndrome. *Dermatol Online J* 2010;16:7, with permission from the New York University Department of Dermatology, Dermatology Online Journal, and Dr. Karem Ortega (University of São Paulo-Brazil). (F): Multiple endocrine neoplasia syndrome 1. Reprinted from Darling TN, Skarulis MC, Steinberg SM, Marx SJ, Spiegel AM, Turner M. Multiple facial angiofibromas and collagenomas in patients with multiple endocrine neoplasia type 1. *Arch Dermatol* 1997;133:853–857, with permission from the American Medical Association. (G): Multiple endocrine neoplasia syndrome 2B. Reprinted from Lee YJ, Liu HC, Lee HC, Tzen CY, Huang CY, Yang TL. Picture of the month. Multiple endocrine neoplasia 2B syndrome. *Arch Pediatr Adolesc Med* 2001;155:845–846 and Schaffer JV, Kamino H, Witkiewicz A, McNiff JM, Orlow SJ. Mucocutaneous neuromas: an underrecognized manifestation of PTEN hamartoma-tumor syndrome. *Arch Dermatol* 2006;142:625–632, with permission from the American Medical Association. (H): Tuberous sclerosis complex. (I): Gardner syndrome. Reprinted from Ben Lagha N, Galeazzi JM, Chapireau D, Oxeda P, Bouhnik Y, Maman L. Surgical management of osteoma associated with a familial Gardner's syndrome. *J Oral Maxillofac Surg* 2007; 65:1234–1240, with permission from Elsevier. (J): Muir-Torre syndrome. Reprinted from Marazza G, Masouyé I, Taylor S, Prins C, Gaudin T, Saurat JH, French LE. An illustrative case of Muir-Torre syndrome: contribution of immunohistochemical analysis in identifying indicator sebaceous lesions. *Arch Dermatol* 2006;142:1039–1042, with permission from the American Medical Association.

Table 1. Summary of dermatologic findings of genetic syndromes

Faciocutaneous findings	Location of lesions	Onset of lesions	Additional characteristics	Complications	Genetic Cause
Lentiginosis related					
Peutz-Jeghers syndrome	Lips, oral mucosa, nostrils, limbs, digits, palms, soles, or diffusely over the body	From infancy, fading in adulthood	Gastrointestinal hamartomatous polyps	Intussusception, cancer of the gastrointestinal tract and breasts	Mutations in the tumor suppressor gene <i>LKB1/STK11</i> (serine/threonine kinase gene on 19p13.3)
Carney complex	Vermilion border of the lips, nasal bridge, conjunctiva	Prepubertal, fading after forty	Cardiac and cutaneous myxomas, endocrine abnormalities	Cardiac obstruction and sequelae	Mutations in regulatory subunit 1 α of tumor-suppressor protein kinase A (<i>PRKARIA</i> on 17q22–24)
Photosensitivity related					
Bloom syndrome	Sun-exposed areas	From infancy	Telangiectases, growth deficiency, hypogonadism, immunodeficiency	Lung disease, susceptibility to neoplasia	Mutations in the RecQ helicase-like gene (<i>BLM</i> on 15q26.1)
Rothmund-Thomson syndrome	First on cheeks, followed by extremities and buttocks	From first year of life	Cataracts, developmental delays, dysmorphic features, short stature, microcephaly	Predisposition to cancers	RTS II: Mutations of the RecQ helicase-like 4 (<i>RECQL4</i> on 8q24.3); RTS I: Unknown
Hamartoma related					
Cowden syndrome	Surrounding mouth, nose, and ears	By third decade	Acral and palmoplantar keratoses, café-au-lait spots, vitiligo-like hypopigmentation	Increased risk for breast, thyroid, and endometrial cancers as well as colon polyps	Mutations in phosphatase and tensin homolog gene (<i>PTEN</i> , on 10q23.3) as well as <i>KILLIN</i> hypermethylation
MEN syndrome	Face, trunk and upper extremities (MEN1); lips, tongues, sclera and eyelids (MEN2B)	Third to fifth decades (MEN1); first decade (MEN2B)	Lipomas (MEN1); mucocutaneous neuromas, café-au-lait spots, facial lentigines, and hyperpigmentation of the hands and feet (MEN2B)	Hyperparathyroidism, endocrine gastrointestinal tract adenomas and pituitary adenomas; thyroid carcinoma, pheochromocytoma (MEN2)	MEN1: Mutations in <i>MEN1</i> gene on 11q13; MEN2: Mutations in <i>RET</i> proto-oncogene gene on 10q11.2
Tuberous sclerosis complex	Nose, nasolabial folds, cheeks, and chin in a butterfly or unilateral distribution	From birth and throughout life	Café-au-lait spots, hypopigmented hair, ungual or subungual fibromas, shagreen patches, ash-leaf macules	Seizures, developmental delay, intellectual disability, autism, kidney angiomyolipoma, cardiac rhabdomyoma, pulmonary lymphangioleiomyomatosis	Mutations in tumor suppressors hamartin on 9q34 and tuberin on 6p13.3
Gardner syndrome	Face, scalp, and extremities	Around puberty	Fibromas, lipomas, leiomyomas, pilomatricoma, neurofibroma, congenital hypertrophy of the retinal pigment epithelium, pigmented skin lesions	Adenomatous colon polyps, colorectal cancer, osteoma; cancers of brain, thyroid, liver, duodenum, and kidneys	Mutations in the adenomatous polyposis coli gene (<i>APC</i> on 5q21–22), which interferes with the Wnt-signalling pathway
Muir-Torre syndrome	Face, eyelids, scalp, and trunk	Third decade and later		Gastrointestinal and genitourinary cancers	Mutations in DNA mismatch repair genes: <i>MLH1</i> on 3p21.3 and <i>MSH2</i> on 2p22-p21

Abbreviations: MEN, multiple endocrine neoplasia; RTS, Rothmund-Thomson syndrome.

adenomas [16]. Multiple facial angiofibromas in these two syndromes present as small (0.1–0.3 cm), reddish-brown, smooth papules typically over the nose, nasolabial folds, cheeks, and chin in a butterfly distribution or unilateral distribution, appearing during childhood (Figs. 1F, 1H, 2F, 2H). Most angiofibromas are benign, but they can cause disfigurement and aesthetic concerns.

Besides multiple facial angiofibromas, multiple cutaneous collagenomas and lipomas are also common in patients with MEN1, but they are usually located on the trunk and upper extremities [16]. Although the prevalence of these cutaneous lesions varies among different ethnic groups, the combination of more than three angiofibromas along with collagenomas has a high sensitivity and specificity for the diagnosis of MEN1 [13].

MEN2B is another subtype of MEN syndrome. The

common concomitant tumors in MEN2B are medullary thyroid carcinoma (a form of thyroid cancer) and pheochromocytoma, which is a tumor of the adrenal glands that can cause dangerous hypertension. MEN2B is characterized by the additional presence of mucocutaneous neuromas, the most consistent and distinctive feature appearing in the first decade of life in almost 100% of patients. The neuromas usually appear as yellowish-white or skin-colored painless, raised bumps on the lips or tongue (Figs. 1G, 2G). Large numbers of neuromas on the lip or the anterior dorsal surface of the tongue can cause a “blubbery lip” or “frogspawn-like tongue” appearance (Fig. 2G) [17]. Neuromas may also be seen on the sclera and eyelids, sometimes causing the lid to turn inside out.

Gardner syndrome, a subtype of familial adenomatous polyposis (FAP), is characterized by the presence of thou-

sands of polyps in the colon as well as osteomas and skin/soft-tissue tumors [18]. Without early detection, FAP is a life-threatening condition, as, in virtually 100% of cases, the polyps under malignant change by the fourth decade of life if the colon is not resected [19]. Epidermoid cysts are the main faciocutaneous findings in Gardner syndrome. They are circumscribed, firm, slow-growing lumps within the dermis, having a distinct membrane with the nearby tissue. These cysts contain soft, cheesy-like skin secretions (keratin; Fig. 1I). They often occur in puberty, earlier than ordinary cysts, and in unusual locations such as the face, scalp, and extremities [20]. In addition, they tend to occur in multiples for more than half of patients; combined with the early age of onset, this is the most notable characteristic of Gardner syndrome (Figs. 1I, 2I). These cysts are usually asymptomatic; however, in some cases they may be pruritic, inflamed, or ruptured. Other skin findings of Gardner syndrome are fibromas, lipomas, leiomyomas, pilomatricomas, neurofibromas, and pigmented skin lesions (Table 1).

Sebaceous gland neoplasms are uncommon cutaneous tumors in the general population, but they are the most characteristic dermatologic markers of Muir-Torre syndrome (MTS), a subtype of hereditary nonpolyposis colorectal cancer syndrome [21]. MTS is identified by at least one sebaceous skin tumor or keratoacanthoma and one or more visceral malignancies, with an increased propensity for colorectal and genitourinary cancers [22]. Sebaceous gland neoplasms in MTS can precede the presentation of internal malignancy, although they often develop later. These neoplasms usually present as multiple yellow papulotubercular lesions and are most often located on the face, eyelids, scalp, and trunk (Figs. 1J, 2J). Sebaceous carcinomas most commonly occur on the eyelids, appearing as firm, yellow nodules with a tendency toward ulceration; they can invade the orbit, metastasize, and cause death [23]. Clinically, these lesions are often mistaken for chalazia, chronic blepharoconjunctivitis, or carbuncles.

Keratoacanthoma is also a characteristic lesion in MTS. It is a relatively low-grade malignancy and usually considered to be a variant of squamous cell carcinoma. Keratoacanthoma appears as small pimple-like bumps with a central crater-like growth. It can occur anywhere on the body, with the most common sites being the face, eyelids, and dorsum of the hands. Keratoacanthoma with sebaceous differentiation, whether solitary or multiple, is strongly associated with MTS; comprehensive screening of MTS-associated cancers should be considered [24].

CONCLUSION

Here we present some examples of faciocutaneous findings that can serve as early markers for multisystem genetic disorders with visceral cancer predisposition. For some genetic syndromes, early diagnosis may even prove to be lifesaving. For example, there is nearly 100% polyp malignancy in Gardner syndrome if the colon is not resected; intracardiac obstruction and even myocardial infarction of cardiac myxoma may occur with Carney complex.

The main characteristic faciocutaneous clues to genetic syndromes with cancer predisposition are as follows:

1. Symmetrically located in the periorbital area (e.g., lentigines with Carney complex), the periorificial region (e.g., lentigines with Peutz-Jeghers syndrome and hamartomas with Cowden syndrome), or on the cheeks (e.g., telangiectatic erythema with Bloom syndrome and Rothmund-Thomson syndrome).
2. Occurring in uncommon numbers (e.g., multiple epidermoid cysts with Gardner syndrome, sporadic sebaceous gland neoplasms with Muir-Torre syndrome).
3. Occurring in uncommon locations (e.g., multiple epidermoid cysts on the face with Gardner syndrome).
4. Positive family history.
5. Analogous facial lesions (occurring with several syndromes, including the multiple facial angiofibromas with MEN1 syndrome and tuberous sclerosis complex).

Disregarding aesthetic concerns, the majority of the facial lesions are asymptomatic, which delays diagnosis and treatment of underlying cancers. However, lesions on the face can be easily observed by patients themselves, their families, friends, colleagues, or physicians. More importantly, most lesions on the face tend to present before or with visceral malignancies, such as lentigines in Peutz-Jeghers syndrome, erythematous/edematous skin plaques in Rothmund-Thomson syndrome, faciocutaneous hamartomas in Cowden syndrome, and mucocutaneous neuromas in MEN2B. Therefore, observations and comparisons of the dynamic changes of these characteristic lesions on the face can be indicative of the development of hiding visceral malignancies.

Faciocutaneous characteristics in these genetic syndromes can remind physicians of the hiding malignancies, but they are not absolute. Objective evaluation of these faciocutaneous clues in combination with other clinical information (e.g. family history, histopathological findings, combination with other concomitant faciocutaneous lesions) is helpful in narrowing the diagnosis range. Some of the faciocutaneous lesions are similar in appearance but histopathologically different beneath the skin, which contributes to the different clinical indications. For example, keratoacanthoma occurs in association with Muir-Torre syndrome or Ferguson-Smith syndrome (self-healing epitheliomata) [25], Grzybowski syndrome (generalized eruptive keratoacanthomas of Grzybowski) [26], or immunosuppressive therapy [27], whereas keratoacanthoma with sebaceous differentiation, whether solitary or multiple, is strongly associated with Muir-Torre syndrome. Most genetic syndromes with visceral cancer predisposition display more than one kind of characteristic faciocutaneous or other cutaneous lesions (Table 1). A combination of these lesions can further complicate early diagnosis. For example, multiple facial angiofibromas, cutaneous collagenomas, and lipomas all have been reported in MEN1. A combination of more than three angiofibromas along with collagenomas is highly sensitive and specific to MEN1.

In conclusion, increased awareness of such faciocutaneous markers can call physicians' attention to underlying multisystem genetic disorders and render earlier screening, detection,

and diagnosis with the help of modern molecular biology. The list of genetic syndromes with faciocutaneous manifestations is still expanding. We look forward to the continued elucidation of faciocutaneous findings in both classic and new genetic syndromes.

AUTHOR CONTRIBUTIONS

Conception/Design: Zhu Shen

Collection and/or assembly of data: Zhu Shen, Jodi D. Hoffman, Fei Hao

Data analysis and interpretation: Zhu Shen, Jodi D. Hoffman, Fei Hao, Eric Pier

Manuscript writing: Zhu Shen, Jodi D. Hoffman, Eric Pier

Final approval of manuscript: Zhu Shen, Jodi D. Hoffman, Fei Hao, Eric Pier

REFERENCES

- Horvath A, Stratakis CA. Carney complex and lentiginosis. *Pigment Cell Melanoma Res* 2009;22:580–587.
- van Lier MG, Wagner A, Mathus-Vliegen EM et al. High cancer risk in Peutz-Jeghers syndrome: A systematic review and surveillance recommendations. *Am J Gastroenterol* 2010;105:1258–1264.
- Hearle N, Schumacher V, Menko FH et al. Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. *Clin Cancer Res* 2006;12:3209–3215.
- Vezzosi D, Vignaux O, Dupin N et al. Carney complex: Clinical and genetic 2010 update. *Ann Endocrinol (Paris)* 2010;71:486–493.
- Carney JA, Headington JT, Su WP. Cutaneous myxomas. A major component of the complex of myxomas, spotty pigmentation, and endocrine overactivity. *Arch Dermatol* 1986;122:790–798.
- Chabosseau P, Buhagiar-Labarchède G, Onclercq-Delic R et al. Pyrimidine pool imbalance induced by BLM helicase deficiency contributes to genetic instability in Bloom syndrome. *Nat Commun* 2011;2:368.
- Simon T, Kohlhase J, Wilhelm C et al. Multiple malignant diseases in a patient with Rothmund-Thomson syndrome with RECQL4 mutations: Case report and literature review. *Am J Med Genet* 2010;152A:1575–1579.
- Larizza L, Roversi G, Volpi L. Rothmund-Thomson syndrome. *Orphanet J Rare Dis* 2010;5:2.
- Stanich PP, Owens VL, Sweetser S et al. Colonic polyposis and neoplasia in Cowden syndrome. *Mayo Clin Proc* 2011;86:489–492.
- Pilarski R. Cowden syndrome: A critical review of the clinical literature. *J Genet Couns* 2009;18:13–27.
- Trufant JW, Greene L, Cook DL et al. Colonic ganglioneuromatous polyposis and metastatic adenocarcinoma in the setting of Cowden syndrome: A case report and literature review. *Hum Pathol* 2012;43:601–604.
- Hamilton HK, Tonkovic-Capin V. Images in clinical medicine. Facial angiofibromas associated with tuberous sclerosis. *N Engl J Med* 2011;364:1061.
- Asgharian B, Turner ML, Gibril F et al. Cutaneous tumors in patients with multiple endocrine neoplasia type 1 (MEN1) and gastrinomas: prospective study of frequency and development of criteria with high sensitivity and specificity for MEN1. *J Clin Endocrinol Metab* 2004;89:5328–5336.
- Ciancio SJ, Vira M, Simon MA et al. Giant bilateral renal angiomyolipomas associated with tuberous sclerosis. *Urology* 2001;57:554.
- Zhang X, Travis WD. Pulmonary lymphangioleiomyomatosis. *Arch Pathol Lab Med* 2010;134:1823–1828.
- Darling TN, Skarulis MC, Steinberg SM et al. Multiple facial angiofibromas and collagenomas in patients with multiple endocrine neoplasia type 1. *Arch Dermatol* 1997;133:853–857.
- Lee MJ, Chung KH, Park JS, et al. Multiple endocrine neoplasia type 2B: Early diagnosis by multiple mucosal neuroma and its DNA analysis. *Ann Dermatol* 2011;22:452–455.
- Juhn E, Khachemoune A. Gardner syndrome: Skin manifestations, differential diagnosis and management. *Am J Clin Dermatol* 2010;11:117–122.
- Parks ET, Caldemeyer KS, Mirowski GW. Gardner syndrome. *J Am Acad Dermatol* 2001;45:940–942.
- Ben Lagha N, Galeazzi JM, Chapireau D et al. Surgical management of osteoma associated with a familial Gardner's syndrome. *J Oral Maxillofac Surg* 2007;65:1234–1240.
- Landis MN, Davis CL, Bellus GA, et al. Immunosuppression and sebaceous tumors: A confirmed diagnosis of Muir-Torre syndrome unmasked by immunosuppressive therapy. *J Am Acad Dermatol* 2011;65:1054–1058.
- Cohen PR, Kohn SR, Kurzrock R. Association of sebaceous gland tumors and internal malignancy: The Muir-Torre syndrome. *Am J Med* 1991;90:606–613.
- Shields JA, Demirci H, Marr BP et al. Sebaceous carcinoma of the eyelids: Personal experience with 60 cases. *Ophthalmology* 2004;111:2151–2157.
- Stoebner PE, Fabre C, Delfour C et al. Solitary subungual keratoacanthoma arising in an MSH2 germline mutation carrier: Confirmation of a relationship by immunohistochemical analysis. *Dermatology* 2009;219:174–178.
- Wee SA. Multiple eruptive keratoacanthomas, de novo. *Dermatol Online J* 2004;10:19.
- Lu PD, Lee A, Cassetty CT et al. Generalized eruptive keratoacanthomas of Grzybowski. *Dermatol Online J* 2009;15:6.
- Dessoukey MW, Omar MF, Abdel-Dayem H. Eruptive keratoacanthomas associated with immunosuppressive therapy in a patient with systemic lupus erythematosus. *J Am Acad Dermatol* 1997;37:478–480.