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Cutaneous manifestations in neuro-oncology: clinically relevant tumor and treatment associated dermatologic findings

Roy E. Strowd[a,b,*], Lindsay C. Strowd[c], Jaishri O. Blakeley[a,b]

[a] Department of Neurology, Wake Forest School of Medicine, Winston Salem, NC
[b] Department of Neurology and Oncology, Johns Hopkins School of Medicine, Baltimore, MD
[c] Department of Dermatology, Wake Forest Baptist Medical Center, Winston Salem, NC

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ABSTRACT

Skin findings are a rare but important aspect of the evaluation and management of patients with tumors of the nervous system. Skin findings have the highest prevalence in genetic tumor syndromes termed neuro-genodermatoses, which include neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2), and tuberous sclerosis. Skin changes are observed in patients with non-syndromic nervous system malignancy, often as a result of pharmacotherapy. The skin may also manifest findings in paraneoplastic conditions that affect the nervous system, providing an early indication of underlying neoplasm, including dermatomyosistis, neuropathic itch, and brachioradial pruritus. In this article, we review the major cutaneous findings in patients with tumors of the brain, spine, and peripheral nervous system focusing on (1) cutaneous manifestations of genetic and sporadic primary nervous system tumor syndromes, and (2) paraneoplastic neurological syndromes with prominent cutaneous features.

1. Introduction

The nervous and integument systems are intimately linked. Somatic peripheral nerves carry sensory information to cutaneous dermatomes via alpha-Beta, alpha-Delta, and C fibers, which terminate in the sensory apparati of the skin. Sympathetic and parasympathetic nerves control piloerection, eccrine skin gland function, and subcutaneous vascular tone. Biologically, melanocytes are derivatives of the neural crest and share neuroembryonic origins with nervous tissues contained within the brain and spinal cord.

Hence, while rare, cutaneous manifestations of neuro-oncology are clinically relevant and potentially biologically important features of many tumors of the central nervous system (CNS) and peripheral nervous system (PNS). Skin findings are most prevalent in the genetic neuro-oncologic tumor syndromes. In neurofibromatosis type 1 (NF1) and tuberous sclerosis, cutaneous findings contribute to the criteria used to make the clinical diagnoses. In neurofibromatosis type 2 (NF2) and other rarer tumor syndromes, skin findings can be the first signs of disease providing an important early indication of an underlying tumor syndrome (Supplemental Table and Supplemental Fig. 1). Skin findings are rarely observed in patients with sporadic primary tumors of the brain and spinal cord (eg, generalized and localized isolated pruritus, brachioradial pruritus, and trigeminal trophic syndrome). However, ongoing investigation of biologically targeted agents for neuro-oncology indications has resulted in an increased frequency of treatment-related skin changes in neuro-oncology. Cutaneous manifestations may also be present in paraneoplastic neurological syndromes and herald an underlying malignancy.

In this article we review the major cutaneous findings in patients with nervous system tumors focusing specifically on (1) cutaneous features of the genetic and sporadic primary tumor syndromes, and (2) cutaneous manifestations of paraneoplastic neurological syndromes.

2. Cutaneous findings in neurogenetic tumor syndromes

2.1. Neurofibromatosis type 1

Neurofibromatosis type 1 (NF1) is the most common single mutation genetically inherited neurologic disorder affecting approximately 1 in 2,500–4,000 live-births [1]. This tumor-suppressor syndrome results from loss of function of the neurofibromin protein encoded by the *NF1* gene on chromosome 17 (17q11.2) [2]. Germline mutation in the *NF1* gene results in a clinical syndrome that can impact the skin, bones, eyes,

* Corresponding author. Johns Hopkins, Cancer Research Building, 1M16, Baltimore, MD 21287. Tel.: +410-955-8837; fax: +410-614-9335.
E-mail address: rstrowd@wakehealth.edu (R.E. Strowd).

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Table 1
Clinical criteria established by the NIH for the diagnosis of NF1.

Patient needs 2 or more of the following:
1. ≥6 café au lait macules >0.5 cm in diameter in prepubescent children >1.5 cm in diameter in post-pubertal children
2. Intertriginous (ie, axillary or inguinal) freckling
3. Two or more dermal neurofibromas or 1 plexiform neurofibroma (pNF)
4. Optic pathway glioma (OPG)
5. ≥2 Lisch nodules (iris hamartomas)
6. Presence of specific bony dysplasia: sphenoid wing dysplasia, thinning of long bones with or without pseudoarthrosis (ie, false joint)
7. A 1st-degree relative with confirmed NF1

NIH = National Institutes of Health; NF1 = neurofibromatosis type 1.
Adapted from Gutmann DH, et al 1997[3] and the NIH Consensus Statement.[4]

vasculature, and the CNS and PNS. The hallmark of this condition is the development of benign tumors of the skin and the peripheral nerve sheath: cutaneous and plexiform neurofibromas. While gene testing of *NF1* is used in select cases to establish a diagnosis, most patients are diagnosed clinically using criteria that focus on cutaneous findings and has been established by National Institutes of Health (Table 1) [3, 4].

Cutaneous findings are common in patients with NF1 but vary over a patient's lifetime [5]. Café au lait macules present as flat tan patches with no appreciable texture or scaling and are common at birth (Fig. 1A). Typical café au lait macules of NF1 have uniform pigmentation with distinct, regular borders, in contrast to those with irregular borders or nonhomogeneous pigmentation, which is atypical for NF1. These lesions are frequently brought to the attention of pediatricians by a child's parents as they are the most universal findings and often the first sign of disease. While many children with isolated café au lait macules are referred to specialty clinics to rule out NF1, most will not develop NF1. Comprehensive dermatologic evaluation is helpful as studies show that defining the number and appearance (ie, typical *v* atypical) of café au lait macules has important predictive value for diagnosis. In one epidemiologic study, 77% of patients with six or more café au lait macules at presentation ultimately met clinical criteria for diagnosis of NF1 by study end with the most common confirmatory findings being intertriginous freckling (77%), Lisch nodules (18%), or plexiform neurofibroma (6%). Lesion appearance was important with less than 5% (or 2/42 patients) of patients with atypical lesions ultimately meeting criteria for NF1 [6]. In cases of diagnostic uncertainty such as with isolated café au lait macules without confirmatory findings for NF1, genetic testing is available but best performed in the setting of a genetic or multidisciplinary clinic specializing in the care of NF1 patients. Other skin manifestations of NF1 include small pigmented macules in the axillae or groin skin, which has been termed Crowe's sign (Fig. 1D) [7]. Cutaneous neurofibromas (cNFs) are superficial tumors of the peripheral nerve sheath which manifest as skin-colored or slightly pink-brown soft papules and nodules. These lesions invaginate when compressed, a finding that has been termed the "button-hole" sign [8]. Most cNFs are painless though a subset may present with pain exacerbated by palpation. Cutaneous neurofibromas are less common in childhood and typically begin to appear in adolescence. Unlike café au lait macules which may fade during adulthood, cNFs can increase in size and number throughout life. In severe cases hundreds of lesions may develop, causing substantial disfiguration and psychosocial distress (Fig. 1B). Surgical removal can be considered for painful tumors, to correct deforming lesions, or when lesions develop in a problematic region (ie, brassiere line, digits). Lisch nodules are painless pigmented brown hamartomas arising on the iris of the eye. These common lesions develop during adolescence and reach a prevalence of >95% by age 21 [9]. Fortunately, they are not associated with any functional impact.

Oncologic manifestations of NF1 include both nervous and non-nervous system tumors. Non-nervous system malignancies vary in prevalence and include gastrointestinal stromal tumors (occurring in 5%–25%) [10] and neuroendocrine tumors such as pheochromocytoma (occurring in around 15%) [11,12]. Plexiform neurofibromas (pNFs) are the major PNS tumor occurring in approximately 30%–55% of patients [13,14]. These tumors are heterogeneous, and are composed of Schwann cells and neuronal axons, fibroblasts, macrophages, mast cells, perineural cells, and extracellular matrix [15]. Plexiform neurofibromas may be isolated to the deep nerves, may involve the skin, or may have a combination of deep and superficial components. Similarly, their radiographic appearance may be diffuse, nodular, or a combination of both. When deep, they are composed of multiple hypertrophic nerve sheaths grouped together and may have a "bag of worms" texture upon palpation. Cutaneous involvement manifests as thickening and discoloration of the skin surface (Fig. 1C). While they can occur at any location in the body, they are most frequently found in the head and neck region (25%–38%), followed by the extremities (22%–30%), trunk (16%–17%), and paraspinal area (12%–29%) [16, 17]. In contrast to cNFs, plexiform lesions are a common source of neuropathic pain and in some cases neurologic dysfunction with sensory loss or motor dysfunction [18]. The lifetime risk of malignant transformation to malignant peripheral nerve sheath tumor (MPNST) is 8%–13% and there is suggestion of a worse prognosis than what is experienced with sporadic MPNST [19]. A high index of suspicion and evaluation by a multidisciplinary team using neuroimaging and histopathologic evaluation of tissue are necessary for pNFs that present with new pain or rapid growth to ensure that they are not undergoing malignant transformation [20–22]. In the CNS, though tumors do occur throughout the cortex and brainstem, optic pathway gliomas (OPGs) account for the majority of CNS neoplasms and are present in up to 15%–20% of NF1 children [23–25]. Yearly ophthalmologic evaluation is used to screen for these lesions until age >10 years, after which the majority will remain stable or occasionally regress [26]. Screening neuroimaging is controversial, but generally not pursued unless patients develop loss of visual acuity, proptosis, precocious puberty, or visual field deficits [27]. In those with known lesions, radiographic surveillance with gadolinium-enhanced magnetic resonance imaging (MRI) of the brian (with orbits) in combination with regular ophthalmologic evaluation is recommended. The majority of OPGs are indolent with two thirds never requiring treatment [28, 29].

2.2. *Neurofibromatosis type 2*

Neurofibromatosis type 2 (NF2) is an autosomal dominant tumor-suppressor syndrome less common than NF1 affecting 1 in 33,000–40,000 live births [29]. Mutation in the *NF2* gene on chromosome 22 (22q12) results in loss of functioning merlin or schwannomin protein and contributes to nervous system tumors, including meningiomas, ependymomas, and spinal and cranial nerve schwannomas. The National Institutes of Health (NIH) clinical diagnostic criteria include: (1) the presence of bilateral vestibular schwannomas, or (2) a family history of NF2 and either unilateral vestibular schwannoma or any two other tumors associated with NF2, including the presence of a juvenile posterior subcapsular cataract [30, 31]. Bilateral vestibular schwannomas are pathognomonic for NF2 and present with hearing loss, tinnitus, balance difficulty, and rarely vertigo. Intracranial or spinal meningiomas are present in approximately 50% of patients and are benign World Health Organization (WHO) grade I lesions [32]. In

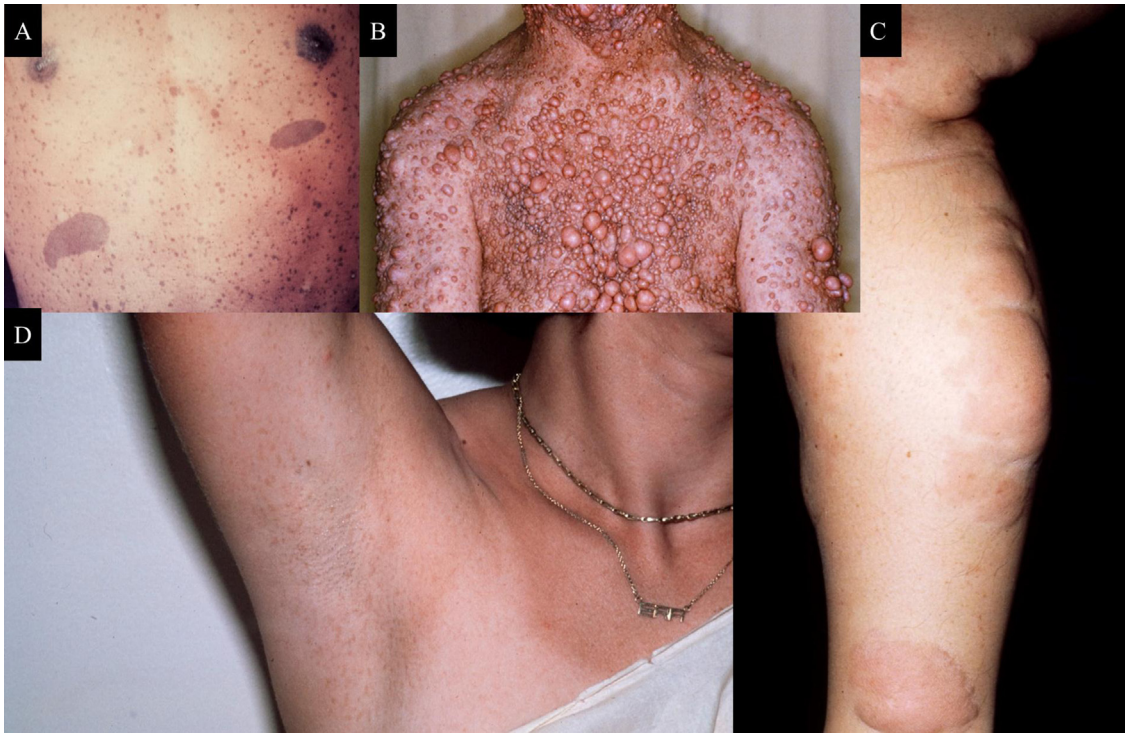

Fig. 1. Major cutaneous manifestations of NF1. (A) Café au lait macules in an NF1 patient; (B) numerous diffuse cutaneous neurofibromas in an NF1 patient; (C) the superficial skin appearance of a plexiform neurofibroma extending from thigh to ankle on the posterior aspect of the leg in an NF1 patient; and (D) Crowe's sign or axillary freckling in an NF1 patient.

contrast to sporadic meningiomas, patients with NF2 often possess multiple intra- or extracranial lesions and meningiomatosis [33]. Spinal ependymomas are present in 33%–53% of patients but are typically asymptomatic, indolent, WHO grade I neoplasms located at the cervicomedullary junction or cervical spine [32].

Cutaneous manifestations are more subtle in NF2 than in NF1. Café au lait macules and dermal tumors are seen and in some cases may be the earliest observable manifestations of disease [34]. Epidemiologic studies suggest that up to 70% of patients with NF2 have skin tumors, though only 10% harbor more than 10 lesions [35]. Cutaneous tumors in NF2 are usually schwannomas, derived from myelin producing Schwann cells of the peripheral nerves, though neurofibromas similar to those occurring in NF1 do occur [36]. The schwannomas may develop superficially and appear as slightly raised areas of pigmented skin with excess hair. Deeper lesions are also observed and present as focal or fusiform swelling of a palpable nerve [35]. NF2-associated cutaneous schwannomas may be asymptomatic or produce severe dysesthetic pain necessitating systemic pharmacotherapy, regional nerve block, or in select refractory cases surgical removal of the causative lesion.

2.3. *Tuberous sclerosis complex*

Tuberous sclerosis complex (TSC) is another autosomal dominant tumor-suppressor syndrome characterized by benign hamartomas of the skin, brain, heart, and kidney, as well as cognitive deficits, neurobehavioral abnormalities (eg, autism), and epilepsy [37] (Table 2). Two disease causing genes have been identified including the *TSC1* gene on chromosome 9 (9q34) and *TSC2* on chromosome 16 (16p13), which encode hamartin and tubulin, respectively [38, 39].

Tuberous sclerosis, similar to NF1, has numerous skin findings which arise at different stages of development. The earliest cutaneous sign is the presence of "ash leaf spots", which can present at birth (Fig. 2A). These hypopigmented nonscaling small macules or patches are reported in over 95% of TSC patients and easily visualized in patients with a darker baseline skin tone [40]. In those with paler skin tones, the use of a Woods lamp (ultraviolet light) can illuminate subtle lesions. The presence of three of more hypomelanotic macules is suggestive of TSC (Fig. 2D). Facial angiofibromas, the second most common skin manifestation of TSC, present as clusters of multiple small monomorphic brownish-red papules, which appear almost acneiform on the nose and cheeks starting in childhood (Fig. 2B) [40]. These lesions can be quite disfiguring in more severe cases (Fig. 2C). Treatment includes dermabrasion (sanding of the skin), laser ablation, or topical rapamycin. Periungual fibromas, also known as Koenen's tumors, are skin-colored papules that grow on cuticular skin of hands and feet (Fig. 2E). They appear around puberty and the main method of treatment is surgical excision. The Shagreen patch, a connective tissue nevus, appears as a skin colored or slightly hyperpigmented plaque with firm texture. The induration of the

Table 2
Cutaneous and mucosal criteria for the diagnosis of TSC.

Major criteria	Minor criteria
Cutaneous diagnostic criteria	
• 3 or more ash leaf macules > 5-mm in diameter • 3 or more facial angiofibromas or a fibrous cephalic plaque • 2 or more ungula fibromas • Connective tissue nevus (eg, Shagreen patch)	• Confetti macules • 2 or more oral fibromas • 3 or more dental enamel pits

Note café au lait macules are observed but not included in the diagnostic criteria. In addition, extracutaneous diagnostic criteria include multiple retinal hamartomas, cortical tubers, subependymal nodules, subependymal giant cell astrocytomas, cardiac rhabdomyomas, lymphoangioleiomyomasis, and two or more aniomyolipomas (major), as well as retinal achromic patch, multiple renal cysts, and nonrenal hamartomas (minor). Table adapted from Northrup et al 2013 [36].

Fig. 2. Major cutaneous manifestations of tuberous sclerosis complex (TSC). Cutaneous manifestations in tuberous sclerosis complex (TSC) including: (A) ash leaf macule, (B) facial angiofibromas, (C) facial angiofibromas and forehead plaque, (D) multiple ash leaf macules, (E) Koenen's tumors or periungual fibromas, and (F) intraoral fibromas.

Shagreen patch can give the skin a dimpled peau d'orange (French for "skin of an orange") appearance. These lesions frequently occur asymmetrically over the dorsal trunk often in the lower back and are observed in about 50% of patients with TSC [40]. Confetti macules are collections of tiny hypopigmented macules grouped together on the skin. Less common skin findings in TSC include the presence of molluscum fibrosum pendulum (ie, soft pedunculated growths on the neck), café au lait macules, or a forehead plaque (Fig. 2C). Tuberous sclerosis complex can also affect the mucosal skin, with development of fibromas similar to those found on the face and cuticular skin [41]. These are most commonly seen on gingival mucosa but can occur on any intraoral mucosal surface (Fig. 2F). Pits in the enamel of the teeth can also be seen.

Oncologic manifestations of TSC include cortical tubers, subependymal nodules, and subependymal giant cell astrocytomas. Cortical tubers are present in approximately 70% of patients with TSC and represent areas of non-neoplastic cortical dysplasia [42]. The cortical location results in a propensity to epileptogenesis and contributes to the 85% incidence of epilepsy in TSC [43]. Subependymal nodules are benign hamartomas composed of abnormal glia and vascular tissue covered by an ependymal lining. They are often located between the head of the caudate and lateral ventricle [44]. These lesions appear as hyperintensities on T2-weighted MRI imaging and do not enhance with contrast administration. In contrast, subependymal giant cell astrocytomas do typically enhance with contrast. Surgical resection is often the only treatment needed for these WHO grade I gliomas.

3. Cutaneous findings in sporadic neuro-oncologic disease

While cutaneous features herald an underlying nervous system neoplasm in genetic nervous system tumor syndromes, systematic skin findings are much less common in patients with sporadic CNS or PNS tumors. Systemic metastasis is not typical of primary brain tumors [45, 46] and metastatic spread to the skin is exceedingly rare. Reports have described local spread to the adjacent scalp [47, 48] in some cases with skin seeding around the time of operative intervention [48, 49]. Distant cutaneous metastasis has been reported but is exceptional [50,51]. Accordingly, skin checks surveying for cutaneous involvement are not routinely performed.

Hence, few studies have prospectively evaluated cutaneous findings in patients with sporadic primary brain tumors. A study published in 1975 presented data on cutaneous findings in 77 patients with primary (86%), secondary (4%), and other brain tumors (10%, excluding tumors of the hypophysis). Skin findings attributable to the tumors were prevalent in 32% of patients. The authors grouped these into (1) complaints of pruritus (present in 54% of patients), (2) pigmentary changes (29% of patients), and (3) hyperkeratotic changes (27% of patients) [52]. Lesion size, intracranial pressure, and medications were not reported, which may have impacted the results in this study published prior to the era of widespread incorporation of neuroimaging and early detection of these tumors. In 2002, a prospective study of 107 patients with either primary brain tumors or paraneoplastic neurological syndrome clinically assessed for the presence of palmar erythema [53]. Significant erythema was present in 6.5% of patients and slight or localized erythema in 18.5%. These incidence rates were described as similar to those in liver diseases, pregnancy, and rheumatoid arthritis [53]. Thus with the exception of the three discrete syndromes described below, cutaneous findings in patients with primary brain or spinal cord tumors should prompt a comprehensive medical and dermatologic evaluation with attention paid to comorbid medications, effects of radiation therapy, and other factors that may contribute to dermatologic complaints.

3.1. *Neuropathic itch*

Neuropathic itch is a pathologic form of itch where the itch sensation is either out of proportion to the pruritogenic stimulus or present without any cutaneous stimulation at all. This form of itch can be severe, difficult to treat, and disabling to patients.

A variety of neurologic conditions affecting peripheral nerves are associated with neuropathic itch (radicular nerve root compression, shingles and other neurosensory ganglionopathies, small fiber polyneuropathy, etc). Brain and spinal cord lesions (eg, stroke, multiple sclerosis, brain abscess) have also been associated with neuropathic itch [54]. In cases of CNS pathology, disruption of normal nociceptive transmission is thought to result in distortion of the stimulus-response curve and patients present with focal or generalized pruritus [55].

In patients with primary CNS tumors, neurogenic pruritus is an uncommon but reported finding. Four case reports describe three pediatric patients and one adult who presented with isolated, dermatomally localized neuropathic itch without neurologic deficit. In these patients, subsequent biopsy (n = 3) or radiographic diagnosis (n = 1) of an intramedullary neoplasm was made including one ganglioglioma, two pilocytic astrocytomas, and one unspecificied intramedullary glioma [56–59]. In addition, systemic lymphoproliferative malignancies which may infiltrate peripheral nerves are associated with diffuse whole-body pruritus [60]. Thus in rare cases of unexplained localized or diffuse pruritus without etiologic explanation despite comprehensive evaluation, neurologic workup is not unreasonable.

3.2. Brachioradial pruritus

Brachioradial pruritus (BRP) is a localized form of neuropathic itch where patients present with unilateral or bilateral intense itching, burning, tingling, or crawling sensation on the skin of the arms. The most common distribution is the skin on the forearms but can involve the entire arm. On skin exam there are no primary lesions but many secondary findings of ecchymoses, linear excoriations, picker's nodules, and scarring (Supplemental Fig. 2A). This condition arises from disruption of C fiber sensory transmission from pathology in the cervical spine. Cervical radiculopathy and myelopathy are the most common neurologic association, and the clinical presentation may be due to spinal cord tumors in rare instances [61]. Many of these patients are diagnosed with eczema or dry skin due to the lack of primary skin findings, but the presence of significant itching and burning out of proportion to exam findings should alert the physician to the possibility of BRP. Symptoms typically resolve with treatment of the underlying cause of the cervical radiculopathy [62]. Other treatment options include topical capsaicin, oral neuromodulating medications like amitriptyline, gabapentin and pregabalin, and physical therapy [63].

3.3. Trigeminal trophic syndrome

Trigeminal trophic syndrome (TTS) is a rare but severely disfiguring form of localized neuropathic dysfunction affecting patients with an insult to the trigeminal nerve. TTS typically presents following trigeminal injury from diseases such as ischemic stroke, trauma, and trigeminal nerve ablation, but can also be idiopathic and has been rarely reported in patients with brain tumors [64–66]. Disruption of normal trigeminal nerve sensory transmission results in severe pruritus, tingling, and pain. These symptoms cause the patient to pick and mutilate the skin overlying the trigeminal nerve distribution. TTS presents as unilateral non-healing ulcerations and linear excoriations affecting the nasal ala, medial cheek, and forehead (Supplemental Fig. 2B). Often TTS goes undiagnosed or misdiagnosed as a herpetic infection, bacterial infection, pyoderma gangrenosum, or cutaneous malignancy. While uncommon, reports have described TTS in patients with glioma, meningiomas and cranial nerve schwannomas, though in these cases postoperative cranial neuropathy was also implicated as a potential causative factor [66–69]. Treatment for TTS involves patient education, treatment of underlying neurologic insult, trigeminal nerve ablation, and topical barrier devices to prevent picking behavior.

4. Cutaneous findings in patients with paraneoplastic neurological syndromes

4.1. Dermatomyositis

Dermatomyositis is an inflammatory myopathy characterized by photosensitive skin changes that coincide or precede the development of proximal muscle weakness. Dermatologic manifestations include a violaceous discoloration of the upper eyelid, called the heliotrope rash; erythema of the chest and upper back called the "shawl sign", and scaly erythematous papules overlying the distal and proximal interphalangeal joints and elbows, termed Gottron's sign and papules [70]. Neurologically, proximal myopathy often follows the onset of rash and features prominent limb- and shoulder-girdle weakness typically accompanied by elevation of serum creatinine kinase levels. Amyopathic variants have also been described and underscore the importance of maintaining an index of suspicion for neurologic manifestations when completing dermatologic evaluation in these patients [71]. Many cases of dermatomyositis represent a pure autoimmune inflammatory condition; though multiple studies have suggested an increased risk of solid organ malignancy in adults with dermatomyositis supporting a paraneoplastic mechanism of disease in up to 25% of cases [72–75]. In these cases, auto-reactive antigens expressed by the tumor itself may give rise to an anti-tumor/anti-self immune response that plays a role in the development of dermatomyositis [76]. Though the number of testable myositis specific antibodies has expanded rapidly in the last decade, none are known to be specific for paraneoplastic dermatomyositis and clinicoradiographic evaluation remains the primary methods of diagnosis and surveillance.

5. Conclusion

Cutaneous findings are a rare but important clinical finding in patients with tumors of the brain, spinal cord, and peripheral nerve. Skin features are most prominent in the genetic tumors syndromes of NF1 and tuberous sclerosis but also should be considered in the evaluation of other genetic nervous system syndromes including NF2. In patients with sporadic nervous system tumors, the incidence of tumor-related cutaneous manifestations appears to be low. While treatment-related skin changes have historically been uncommon with neuro-oncologic chemotherapeutics, the incidence is rising as targeted biologic agents are investigated in these patients and may become important in future clinical care. Dermatomyositis is a prototypical example of a paraneoplastic neurological syndrome with prominent skin findings which precede neurologic dysfunction. Given the range of these many cutaneous findings and the often multiple potential explanations, a multidisciplinary approach to management with collaboration across dermatology, oncology, and primary medicine offers the optimal approach to the evaluation and management of these patients.

Conflicts of interest

None.

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APPENDIX. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1053/j.seminoncol.2016.02.029.

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