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A diagnostic and management algorithm for individuals with an isolated skin finding suggestive of tuberous sclerosis complex

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Dear Editor

Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous syndrome caused by mutations in the *TSC1* or *TSC2* gene, leading to development of hamartomas in the brain, kidneys, heart, lungs, eyes, and skin.^{1–3} A diagnostic evaluation for TSC includes: 1) family history, 2) skin, dental, and eye examination, 3) functional and imaging studies of internal organs depending on patient age and presentation, and 4) consideration of genetic testing.⁴ The decision to pursue a complete evaluation for TSC is readily made for those presenting early in life with multiple complications of the disease. This decision may be more difficult in those who manifest only one skin finding of TSC. In such instances, additional considerations enter the decision-making process, such as concern for causing unnecessary anxiety in the patient or family, possible health risks and financial costs to screen individuals with a seemingly low diagnostic yield, or the potential for misidentification or misattribution of skin lesions that pose little or no problem to the patient. Our goal was to identify situations that should increase suspicion for TSC and others where extensive TSC-related work-up may not be warranted. We evaluated the earliest cutaneous manifestations in a cohort of 115 adults with TSC. Based on these patients and our experience evaluating 13 additional patients screened for TSC, we propose a new algorithm that refines the evaluation of those presenting with one skin finding suggestive for TSC.

A retrospective review of medical records from patients recruited for studies of TSC and lymphangioleiomyomatosis at the National Institutes of Health Clinical Center in Bethesda, Maryland from 1998 to 2015 was performed. This cohort was enriched for patients diagnosed with TSC in adulthood, frequently after complications from renal

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angiomyolipomas or LAM.^{5, 6} Others were referred to our institution for TSC screening and underwent full TSC diagnostic evaluation. Written informed consent was obtained to protocols 00-H-0051, 95-H-0186 and/or 82-H-0032, which were approved by the National Heart, Lung and Blood Institute Institutional Review Board. Individuals were diagnosed based on clinical criteria, and they met updated criteria that outlines a definite diagnosis of TSC as two or more major features or one major feature plus two or more minor features.⁷ Individuals with only one major feature, or two or more minor features, were considered as having “possible” TSC. Skin findings that satisfy major features are hypomelanotic macules (≥ 3 , at least 5 mm in diameter), angiofibromas (≥ 3) or fibrous cephalic plaque, shagreen patch, and ungual fibromas (≥ 2).⁸

Of 115 adults with TSC, 68 (59%) provided a history of manifesting only one cutaneous major feature of TSC for at least one year before onset of any other skin features. During this diagnostic opportunity window, twenty-eight had only hypomelanotic macules, 21 angiofibromas (which were misdiagnosed in 7 patients), 14 fibrous cephalic plaque, 4 shagreen patch and one ungual fibromas. Thirty-five patients (51%) eventually developed AMLs and forty-six (68%) LAM. Median age of manifestation of first cutaneous major feature was 1 year (range 0–20). At time of manifestation, TSC diagnosis was confirmed in 7/68 (10%) patients. Median age of definite TSC diagnosis was 26 years (1–63). Lesion-specific details are presented in Table 1.

Thirteen additional adults were referred to dermatology to evaluate skin findings suggestive of TSC, including facial papules in eight, skin-coloured plaques on the head or trunk in three, and localized hypopigmentation in two. Histopathological analysis excluded TSC in 8 cases. Biopsy showed angiofibromas in one patient; however, adult-onset increased suspicion for Birt-Hogg-Dubé syndrome and identification of trichodiscomas and fibrofolliculomas in family members confirmed this diagnosis. In two cases with multiple small hypopigmented macules, symmetric distribution on the extensor forearms was consistent with idiopathic guttate hypomelanosis. The remaining two patients were given a diagnosis of possible TSC. They had biopsy-confirmed juvenile-onset angiofibromas but no other features to support the diagnosis after full diagnostic evaluation.

In this retrospective analysis, many individuals with TSC initially manifested just one cutaneous major feature and diagnosis was often delayed by insufficient diagnostic evaluation. In other individuals, exemplified by the 11/13 patients in whom TSC was ruled out, it may be possible to avoid comprehensive TSC diagnostic evaluation by detailed skin evaluation. This further characterization of the skin finding as proposed in Figure 1 may also lead to the identification of other diseases in some patients.

Individuals presenting with a skin finding suggestive of TSC should undergo a thorough dermatological examination. In absence of additional TSC skin or oral lesions (dental enamel pits ≥ 3 , intraoral fibromas ≥ 2)^{7, 9}, biopsy may be performed to confirm the clinical diagnosis, particularly as age of presentation increases. The decision to proceed with further work up may be informed by the following classifications: lesions not consistent with TSC, lesions nonspecific or atypical of TSC, and lesions characteristic of TSC (Fig. 1). Lesions not consistent with TSC based on clinical or pathological findings obviate the need

for TSC diagnostic evaluation. When pathology is not sufficient to rule out TSC, history, distribution or configuration can point to alternate aetiologies that may be confirmed by blood studies (e.g. for multiple endocrine neoplasia type 1), DNA testing, or other cost-saving and radiation-sparing measures.^{10, 11} Complete TSC diagnostic evaluation may be performed if less invasive work up is uninformative and certainly for those with skin lesions characteristic of TSC. This decision should not be dissuaded by the fact that the patient feels fine or looks healthy, since internal involvement may be asymptomatic. While confirmation of a pathogenic mutation in *TSC1* or *TSC2* is sufficient for definite diagnosis, imaging is still necessary to determine baseline extent of disease.

In some instances, imaging and genetic testing will be unremarkable. These patients should receive a diagnosis of possible TSC.^{4, 7} We suggest that the patient and/or guardians be informed that the likelihood of disease onset for possible TSC is unknown; therefore, relaying this tentative diagnosis to subsequent caregivers is prudent.^{5, 6} Some patients with no mutation identified using conventional genetic testing may have intronic mutations or mosaicism¹², in which a fraction of cells bear the *TSC1* or *TSC2* mutations. Next generation sequencing of DNA from skin tumours may reveal pathogenic mutations in patients with mosaicism.^{12, 13} Regardless, instructions should be provided regarding signs or symptoms of TSC; those developing new findings may require repeat diagnostic evaluation. Future evaluations may also be considered for paediatric patients, particularly if the initial work-up was performed at a young age before development of detectable disease.

We recommend use of this algorithm to guide the evaluation of patients at the first cutaneous sign of TSC so that treatment, preventative measures, disease counselling and/or plan for lifetime follow-up may be swiftly enacted.^{4, 6, 13, 14}

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References

1. Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. *N Engl J Med*. 2006; 355:1345–56. [PubMed: 17005952]
2. Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. *Lancet*. 2008; 372:657–68. [PubMed: 18722871]
3. Yates JR, Maclean C, Higgins JN, Humphrey A, le Marechal K, Clifford M, et al. The Tuberous Sclerosis 2000 Study: presentation, initial assessments and implications for diagnosis and management. *Arch Dis Child*. 2011; 96:1020–5. [PubMed: 21813552]
4. Krueger DA, Northrup H, International Tuberous Sclerosis Complex Consensus G. Tuberous sclerosis complex surveillance and management: recommendations of the 2012 International

Tuberous Sclerosis Complex Consensus Conference. *Pediatr Neurol.* 2013; 49:255–65. [PubMed: 24053983]

5. Seibert D, Hong CH, Takeuchi F, Olsen C, Hathaway O, Moss J, et al. Recognition of tuberous sclerosis in adult women: delayed presentation with life-threatening consequences. *Ann Intern Med.* 2011; 154:806–13. W-294. [PubMed: 21690595]
6. Nathan N, Burke K, Trickett C, Moss J, Darling TN. The Adult Phenotype of Tuberous Sclerosis Complex. *Acta Derm Venereol.* 2016; 96:278–80. [PubMed: 26258325]
7. Northrup H, Krueger DA, International Tuberous Sclerosis Complex Consensus G. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatr Neurol.* 2013; 49:243–54. [PubMed: 24053982]
8. Teng JM, Cowen EW, Wataya-Kaneda M, Gosnell ES, Witman PM, Hebert AA, et al. Dermatologic and dental aspects of the 2012 International Tuberous Sclerosis Complex Consensus Statements. *JAMA Dermatol.* 2014; 150:1095–101. [PubMed: 25029267]
9. Sparling JD, Hong CH, Brahim JS, Moss J, Darling TN. Oral findings in 58 adults with tuberous sclerosis complex. *J Am Acad Dermatol.* 2007; 56:786–90. [PubMed: 17239986]
10. 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; 133:853–7. [PubMed: 9236523]
11. Schaffer JV, Gohara MA, McNiff JM, Aasi SZ, Dvoretzky I. Multiple facial angiofibromas: a cutaneous manifestation of Birt-Hogg-Dube syndrome. *J Am Acad Dermatol.* 2005; 53:S108–11. [PubMed: 16021156]
12. Tyburczy ME, Dies KA, Glass J, Camposano S, Chekaluk Y, Thorner AR, et al. Mosaic and Intronic Mutations in TSC1/TSC2 Explain the Majority of TSC Patients with No Mutation Identified by Conventional Testing. *PLoS Genet.* 2015; 11:e1005637. [PubMed: 26540169]
13. Tyburczy ME, Wang JA, Li S, Thangapazham R, Chekaluk Y, Moss J, et al. Sun exposure causes somatic second-hit mutations and angiofibroma development in tuberous sclerosis complex. *Hum Mol Genet.* 2014; 23:2023–9. [PubMed: 24271014]
14. Nathan N, Wang JA, Li S, Cowen EW, Haughey M, Moss J, et al. Improvement of tuberous sclerosis complex (TSC) skin tumors during long-term treatment with oral sirolimus. *J Am Acad Dermatol.* 2015; 73:802–8. [PubMed: 26365597]

Figure 1.

Diagnostic and management algorithm for patients with skin findings suggestive of one cutaneous major feature of tuberous sclerosis complex (TSC). Based on skin pathological and/or clinical findings, lesions may be categorized as *not consistent* (red), *nonspecific or atypical* (orange) or *characteristic* (green) of TSC. Some patients with findings nonspecific or atypical of TSC may undergo diagnostic evaluation (dashed arrow) following consideration of other conditions. Patients with skin findings characteristic of TSC should undergo complete diagnostic evaluation.

¹Trichilemmomas (Cowden syndrome), fibrofolliculomas or trichodiscomas (Birt-Hogg-Dubé), trichoepitheliomas (multiple familial trichoepithelioma), sebaceous tumours (Muir-Torre syndrome)

²Piebaldism, Waardenburg syndrome, vitiligo, sarcoidosis, hypopigmented MF, pityriasis alba, leprosy, nevus anemicus, idiopathic guttate hypomelanosis, post-inflammatory hypopigmentation

³Digital mucous cyst, verruca vulgaris, subungual exostosis, subungual corn (heloma), foreign body, pyogenic granuloma, squamous cell carcinoma

⁴Non-familial elastoma or familial elastoma, Buschke-Ollendorff syndrome, nevi, xanthomas, granulomatous disease.

⁵Consider Birt-Hogg-Dubé syndrome or multiple endocrine neoplasia type 1 for patients with adult-onset multiple angiofibromas. Patients with TSC may also present with adult-onset of angiofibromas.

⁶Consider hypomelanosis of Ito for congenital macules arranged in whorls or streaks following Blaschko's lines. Consider nevus depigmentosus (achromicus) for congenital isolated or segmental lesion with serrated border. Patients with TSC may also present with hypopigmented macules of Blaschkoid or segmental morphology. Consider progressive macular hypomelanosis for adolescent or adult onset of nummular, confluent macules concentrated on the trunk.

⁷Consider familial cutaneous collagenoma or eruptive collagenoma. Collagenomas may also be associated with Birt-Hogg-Dubé syndrome or multiple endocrine neoplasia type 1. Multiple storiform collagenomas are observed in Cowden syndrome and volar collagenomas in Proteus syndrome. Buschke-Ollendorff syndrome may present with collagenomas or elastomas. Patients with TSC may also present with small collagenomas on the back.

Table 1

Initial cutaneous major feature in 68 patients with tuberous sclerosis complex.

Initial cutaneous major feature	Patients	Diagnosis confirmed at time of presentation	Median age (years) of manifestation (range)	Median age (years) of diagnosis (range)
Angiofibromas	21	1	5 (1–20)	29 (3–55)
Fibrous cephalic plaque	14	0	0 (0–3)	28 (23–45)
Hypomelanotic macules	28	6	0 (0–10)	21 (0–63)
Shagreen patch	4	0	0.5 (0–4)	32 (18–46)
Ungual fibromas	1	0	20	48