A Non-Epidermolytic Epidermal Naevus of a Soft, Papillomatous Type with Transitional Cell Cancer of the Bladder: A Case Report and a Review of Non-cutaneous Cancers Associated with the Epidermal Naevi

Ellen Flosadóttir[1,4] and Bolli Bjarnason[2–4]

Departments of [1]Odontology and [2]Dermatology, University of Iceland, Vatnsmýrarvegur 16, 101 Reykjavík, Iceland, [3]Department of Dermatology, Karolinska University Hospital, Stockholm, Sweden and [4]Utlitslaekning ehf, Kópavogur, Iceland. E-mail: ellenflosa@hotmail.com

Accepted August 27, 2007.

Sir,

We describe here the case of a man aged 65-years at our first examination with non-epidermolytic epidermal naevus of a soft, papillomatous type covering large areas of the left side of his body and scalp. He reported bilateral hearing loss and earlier frequent mastoiditis. He was of short stature and had had dyspnoea since childhood affecting his sporting activities, reduced touch sensation on the soles of his feet and reduced vibration sensitivity of his toes. His upper teeth were extracted at a young age. He had had amblyopia of the left eye since childhood and an attack of paralysis of that eye. At the age of 22 years, an asymptomatic gross haematuria was discovered caused by a large bladder papilloma at the opening of the left ureter. Lost to follow-up, he presented 2 years later with intermittent gross haematuria and a cancer at the same site. The cancer was confirmed by our review of the pathological report to be of a transitional cell type. The patient had no familial history of epidermal naevi.

The term "epidermal naevus syndrome" has, in the past, been used to refer to the association between epidermal naevi and abnormalities in other organ systems (1). Several distinct birth defects have been lumped together under this designation (2). All epidermal naevus syndromes are mosaic phenotypes (2). Because of the understanding of the concepts of genetic mosaicism, that there are potentially many different epidermal naevus syndromes, or syndromes of which an epidermal naevus is a cutaneous feature, it has been argued that the term "epidermal naevus syndrome" to describe a disease entity should be abandoned (3, 4). Thus far, at least 7 different epidermal naevus syndromes have been identified; viz., naevus sebaceous syndrome, Proteus syndrome, CHILD syndrome, naevus comedonicus syndrome, Becker naevus syndrome, phakomatosis pigmentokeratotica (5, 6); and the last one was first described by Schauder et al. (7) and later termed "angora hair naevus syndrome" (1).

Table I. *Reported cases of epidermal naevi with non-cutaneous cancers*

Reference	Sex	Age at diagnosis of cancer	Type of naevus	Description of malignant tumour
16	M	16 years	EN	Bladder papillary transitional cell carcinoma
17	M	18 years	EN	Transitional cell cancer of urinary tract
18	F	20 years	EN	Transitional cell carcinoma of the bladder
20	F	23 years	EN	Breast adenocarcinoma
20	M	43 years	EN	Oesophageal epidermoid carcinoma
20	M	36 years	EN	Epidermoid carcinoma of unknown origin
21	M	2 years	EN	Astrocytoma
22	N/A	Infancy	EN	Wilms' tumour
23	M	15 months	EN	Bladder rhabdomyosarcoma
24	M	4 years	EN	A yolk sac, papillary adenocarcinoma
25	F	6 years	EN	Wilms' tumour
26	F	32 years	EN	Ameloblastoma
27	M	6 years	EN mixed with a plexiform neurofibroma	Nephroblastoma
28	M	26 years	EN	Embryonal rhabdomyosarcoma
29	M	5 years	NSJ	Adenocarcinoma of parotid glands
30	N/A	N/A	NSJ	Acute lymphocytic leukaemia
30	N/A	N/A	NSJ	Acute lymphocytic leukaemia
30	N/A	N/A	NSJ	Rhabdomyosarcoma
31	F	At birth	LNS	Congenital nephroblastomatosis
32	M	6 years	LNS	Ameloblastoma
33	M	5 years	LVEN	Nephroblastoma
33	N/A	5.5 years	LVEN	Nephroblastoma
34	M	13 years	NUL	"Mixed glioma"
35	M	32 years	UEN	Mucoepidermoid carcinoma of parotid gland
36	M	9 months	UAN	Abdominal neoplasm
37	F	3 years	PS	Endometroid cystadenomatous tumours

EN: epidermal naevus; NSJ: naevus sebaceous of Jadassohn; LNS: linear naevus sebaceous; LVEN: linear verrucous epidermal naevus; NUL: naevus unius lateris; UEN: unilateral epidermal naevus; UAN: unilateral acanthosis nigricans; PS: proteus syndrome; N/A: not available.

 ISSN 0001-5555
doi: 10.2340/00015555-0365

All these patients warrant detailed physical examination at the time of development of the naevus and close follow-up thereafter (8). Surprisingly many have shown systemic malignancies of various origins at a young age (9). We present all reported cases of epidermal naevi we could find with non-cutaneous malignancies by searching Medline (Table I). It is interesting that cancers in the genitourinary tract comprise approximately one-third of all cases reported.

Fibroblast growth factors (FGFs) play a vital role in embryonic development, and mutations of FGFs have been associated with developmental defects in various organ systems (6). It has been suggested that a large proportion of epidermal naevi are caused by a mosaicism of activating FGF receptor 3 (FGFR3) mutations in the human epidermis secondary to a post-zygotic mutation in early embryonic development (10). Interestingly, FGFR3 mutations are also frequent events in papillary urothelial carcinoma (11, 12). The correlation of epidermal neavus and urothelial carcinoma is thought to be non-stochastic and it has been suggested that patients with epidermal naevi and bladder cancer feature a mosaicism of activating FGFR3 mutations (10).

There are many abnormalities of the genitourinary tract that may be associated with the epidermal naevus syndromes, including horseshoe kidney, cystic kidneys, double collecting system, nephroblastomatosis, ureteropelvic junction obstruction, vitamin D resistant rickets, hypospadias, testicular and paratesticular tumours, and cryptorchidism (13). Transitional cell cancer of the bladder is very rare in young people (14, 15). As 3 cases (16–18) of that cancer and epidermal naevi have already been reported, this fourth case makes coincidental association unlikely. The cancer in our case was removed in 1955, but the association between the cancer and the naevus was not noted until many decades later. As this type of cancer appears to be uniformly of a low grade and non-invasive (19) it is possible that some cases have not been reported in the literature.

REFERENCES

1. Happle R, Rogers M. Epidermal nevi. Adv Dermatol 2002; 18: 175–201.
2. Happle R. How many epidermal nevus syndromes exist? A clinicogenetic classification. J Am Acad Dermatol 1991; 25: 550–556.
3. Happle R. Epidermal nevus syndromes. Semin Dermatol 1995; 14: 111–121. Erratum in: Semin Dermatol 1995; 14: 259.
4. Happle R. What is a nevus? A proposed definition of a common medical term. Dermatology 1995; 191: 1–5.
5. Vidaurri-de la Cruz H, Tamayo-Sanchez L, Duran-McKinster C, de la Luz Orozco-Covarrubias M, Ruiz-Maldonado R. Epidermal nevus syndromes: clinical findings in 35 patients. Pediatr Dermatol 2004; 21: 432–439.
6. Sugarman JL. Epidermal nevus syndromes. Semin Cutan Med Surg 2004; 23: 145–157.
7. Schauder S, Hanefeld F, Noske UM, Zoll B. Depigmented hypertrichosis following Blaschko's lines associated with cerebral and ocular malformations: a new neurocutaneous, autosomal lethal gene syndrome from the group of epidermal naevus syndromes? Br J Dermatol 2000; 142: 1204–1207.
8. Rogers M, McCrossin I, Commens C. Epidermal nevi and the epidermal nevus syndrome. J Am Acad Dermatol 1989; 20: 476–488.
9. Solomon LM, Esterly NB. Epidermal and other congenital organoid nevi. Curr Probl Pediatr 1975; 6: 1–56.
10. Hafner C, van Oers JM, Vogt T, Landthaler M, Stoehr R, Blaszyk H, et al. Mosaicism of activating FGFR3 mutations in human skin causes epidermal nevi. J Clin Invest 2006; 116: 2201–2207.
11. Kimura T, Suzuki H, Ohashi T, Asano K, Kiyota H, Eto Y. The incidence of thanatophoric dysplasia mutations in FGFR3 gene is higher in low-grade or superficial bladder carcinomas. Cancer 2001; 92: 2555–2561. Erratum in: Cancer 2002; 94: 2117.
12. Cappellen D, De Oliveira C, Ricol D, de Medina S, Bourdin J, Sastre-Garau X, et al. Frequent activating mutations of FGFR3 in human bladder and cervix carcinomas. Nat Genet 1999; 23: 18–20.
13. Grebe TA, Rimsza ME, Richter SF, Hansen RC, Hoyme HE. Further delineation of the epidermal nevus syndrome: two cases with new findings and literature review. Am J Med Genet 1993; 47: 24–30.
14. Atan A, Basar M, Basar H, Yildiz M, Akalin Z. Transitional cell carcinoma of the bladder in patients under 30 years of age. Int Urol Nephrol 1997; 29: 623–625.
15. Yusim I, Lismer L, Greenberg G, Haomud K, Kaneti J. Carcinoma of the bladder in patients under 25 years of age. Scand J Urol Nephrol 1996; 30: 461–463.
16. Rosenthal D, Fretzin DF. Epidermal nevus syndrome: report of association with transitional cell carcinoma of the bladder. Pediatr Dermatol 1986; 3: 455–458.
17. Rongioletti F, Rebora A. Epidermal nevus with transitional cell carcinomas of the urinary tract. J Am Acad Dermatol 1991; 25: 856–858.
18. Garcia de Jalon A, Azua-Romeo J, Trivez MA, Pascual D, Blas M, Rioja LA. Epidermal naevus syndrome (Solomon's syndrome) associated with bladder cancer in a 20-year-old female. Scand J Urol Nephrol 2004; 38: 85–87.
19. Benson RC, Tomera KM, Kelalis PP. Transitional cell carcinoma of the bladder in children and adolescents. J Urol 1983; 130: 54–55.
20. Pack GT, Sunderland DA. Naevus unius lateris. Arch Surg 1941; 43: 341–375.
21. Meyerson LB. Nevus unius lateralis, brain tumor, and diencephalic syndrome. Arch Dermatol 1967; 95: 501–504.
22. Ross HE. Multiple lytic bone lesions. J Am Osteopath Assoc 1969; 69: 338–345.
23. Dimond RL, Amon RB. Epidermal nevus and rhabdomyosarcoma. Arch Dermatol 1976; 112: 1424–1426.
24. Hornstein L, Bove KE, Towbin RB. Linear nevi, hemihypertrophy, connective tissue hamartomas, and unusual neoplasms in children. J Pediatr 1987; 110: 404–408.
25. Pawlaczyk M, Pietrzak S, Bowszyc-Dmochowska M. [Epidermal nevus syndrome –bi-symptom type]. Chir Narzadow Ruchu Ortop Pol 1996; 61: 505–510. (in Polish).
26. Bazopoulou-Kyrkanidou E, Alexandridis C, Tosios KI, Sotiriadou S, Angelopoulos AP. Epidermal nevus syndrome with development of a mandibular ameloblastoma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000; 90: 64–70.
27. Courville P, Thomine E, Surlemont Y, Hemet J Metayer J, Lauret P. Association d'un naevus épidermique, d'une

neurofibromatose de type 1 et d'un néphroblastome: un nouveau syndrome du naevus épidermique? Ann Pathol 2000; 20: 616–619.
28. Schulz U, O'Leary CP. Spinal AVM, epidermal nevus, and rhabdomyosarcoma: a rare neurocutaneous syndrome? Neurology 2001; 56: 395–397.
29. Berkeley WT. Nevus sebaceus (Jadassohn) complicated by bilateral sailvary gland adenocarcinoma. Plast Reconstr Surg 1959; 23: 55–63.
30. Lanzkowsky P, Shende A. Letter: a possible relationship of nevus sebaceous of Jadassohn (organoid nevus) to childhood malignancies. J Pediatr 1976; 88: 359–360.
31. Lansky LL, Funderburk S, Cuppage FE, Schimke RN, Diehl AM. Linear sebaceous nevus syndrome. Am J Dis Child 1972; 123: 587–590.
32. Lovejoy FH Jr, Boyle WE Jr. Linear nevus sebaceous syndrome: report of two cases and a review of the literature. Pediatrics 1973; 52: 382–387.
33. Raynaud F, Saurat JH. [Epidermal nevus syndrome (Solomon syndrome) in general pediatrics (author's transl)]. Ann Pediatr (Paris) 1982; 29: 46–52. (in French)
34. Andriola M. Nevus unius lateralis and brain tumor. Am J Dis Child 1976; 130: 1259–1261.
35. Curth HO. Die probleme der acanthosis nigricans. Hautarzt 1964; 15: 433–439.
36. Halty M, Delgado BC, Volpé A. Acanthosis nigricans. Revue Sud-Américaine 1933; 3: 189–199.
37. Raju RR, Hart WR, Magnuson DK, Reid JR, Rogers DG. Genital tract tumors in Proteus syndrome: report of a case of bilateral paraovarian endometrioid cystic tumors of borderline malignancy and review of the literature. Mod Pathol 2002; 15: 172–180.