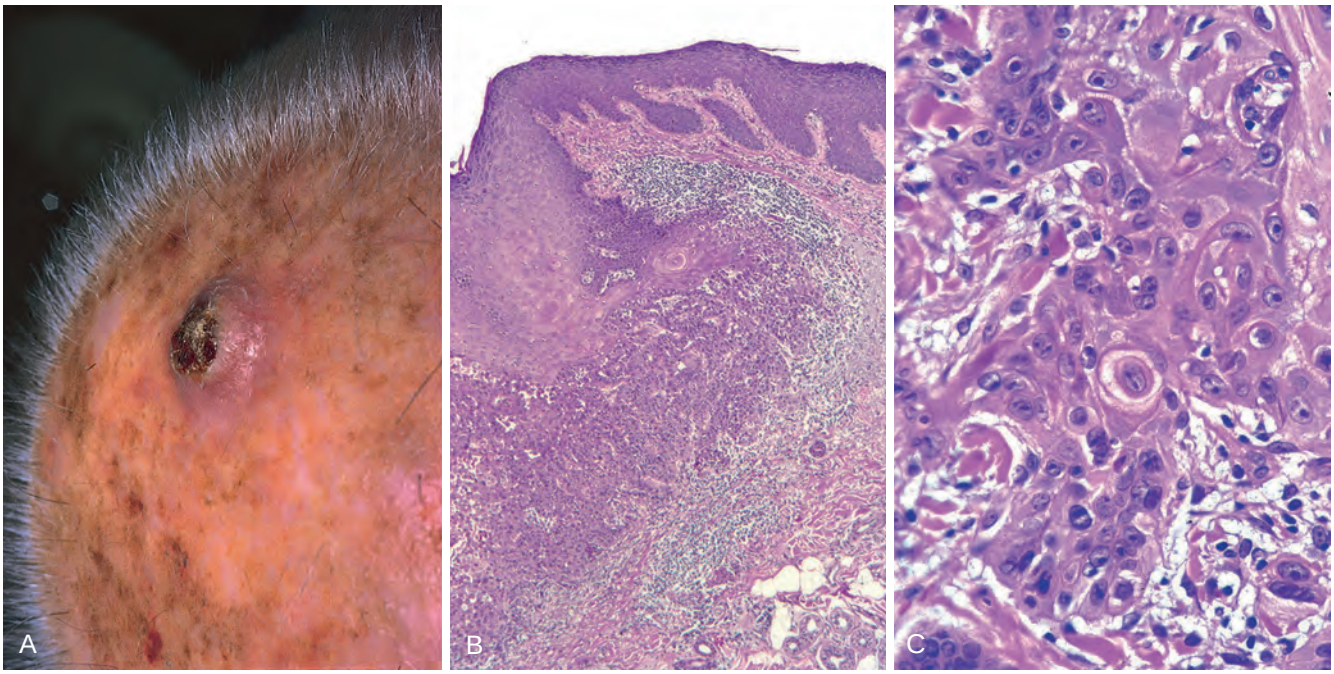

Figure 25-13 Invasive squamous cell carcinoma. **A,** Lesions are often nodular and ulcerated, as seen in this scalp tumor. **B,** Tongues of atypical squamous epithelium have transgressed the basement membrane and invaded deeply into the dermis. **C,** Invasive tumor cells show enlarged nuclei with angulated contours and prominent nucleoli.

NBCCS are born with a germline loss of function mutation in one *PTCH* allele; the second normal allele is inactivated in tumors by a mutation acquired by chance or due to exposure to mutagens (particularly UV light).

PTCH protein is a receptor for *sonic hedgehog (SHH)*, a component of the Hedgehog signaling pathway, which determines polarity during embryonic development and also regulates hair follicle formation and hair growth. In the "off" state, PTCH exists in a complex with another transmembrane protein called SMO (for "smoothened"). Binding of SHH to PTCH releases SMO, which in turn activates the transcription factor GLI1 (Fig. 25-14), thus turning on the expression of genes that support tumor cell growth and survival. Mice engineered to have excessive GLI1 activation are prone to development of skin tumors resembling basal cell carcinomas. Similarly, in NBCCS the loss of PTCH function causes constitutive activation of SMO and GLI1, leading to the development of basal cell carcinoma.

Mutations that activate Hedgehog signaling are also prevalent in sporadic basal cell carcinomas. Loss of function *PTCH* mutations are common, and about one third

Table 25-3 Survey of Familial Cancer Syndromes with Cutaneous Manifestations

Disease	Inheritance	Chromosomal Location	Gene/Protein	Normal Function/Manifestation of Loss
Ataxia-telangiectasia	AR	11q22.3	*ATM*/ATM	DNA repair after radiation injury/neurologic and vascular lesions
Nevoid basal cell carcinoma syndrome	AD	9q22	*PTCH*/PTCH	Developmental patterning gene/multiple basal cell carcinomas; medulloblastoma, jaw cysts
Cowden syndrome	AD	10q23	*PTEN*/PTEN	Lipid phosphatase/benign follicular appendage tumors (trichilemmomas); internal adenocarcinoma (often breast or endometrial)
Familial melanoma syndrome	AD	9p21	*CDKN2*/p16/INK4 *CDKN2*/p14/ARF	Inhibits CDK4/6 phosphorylation of RB, promoting cell cycle arrest/melanoma; pancreatic carcinoma Binds MDM2, promoting p53 function/melanoma; pancreatic carcinoma
Muir-Torre syndrome	AD	2p22 3p21	*MSH2*/MSH2 *MLH1*/MLH1	Involved in DNA mismatch repair/sebaceous neoplasia; internal malignancy (colon and others)
Neurofibromatosis I	AD	17q11	*NF1*/neurofibromin	Negatively regulates RAS signaling/neurofibromas
Neurofibromatosis II	AD	22q12	*NF2*/merlin	Integrates cytoskeletal signaling/neurofibromas and acoustic neuromas
Tuberous sclerosis	AD	9q34 16p13	*TSC1*/hamartin *TSC2*/tuberin	Work together in a complex that negatively regulates mTOR/angiofibromas/mental retardation
Xeroderma pigmentosum	AR	9q22 and others	*XPA*/XPA and others	Nucleotide excision repair/melanoma and nonmelanoma skin cancers

AD, Autosomal dominant; AR, autosomal recessive.
From Tsai KY, Tsao H: The genetics of skin cancer. Am J Med Genet C Semin Med Genet 131C:82, 2004.

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