Melanoma

Lester D.R. Thompson, MD, FASCP

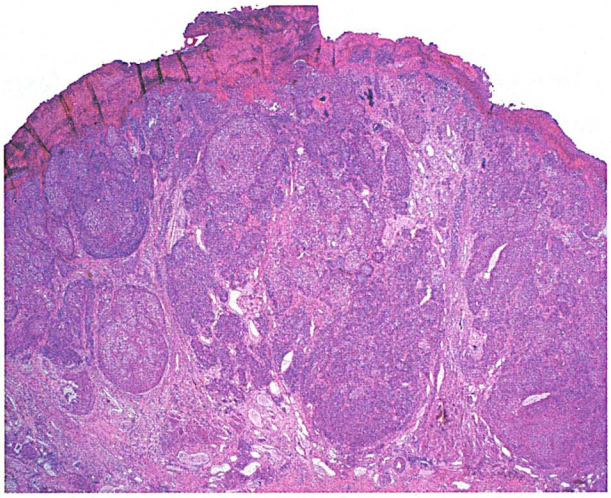

Figure 1. A large melanoma exhibits the typical surface ulceration and asymmetry. Numerous expanded nests and individual cells can be seen filling and expanding both the papillary and reticular dermis. Pigment and inflammation are also visible.

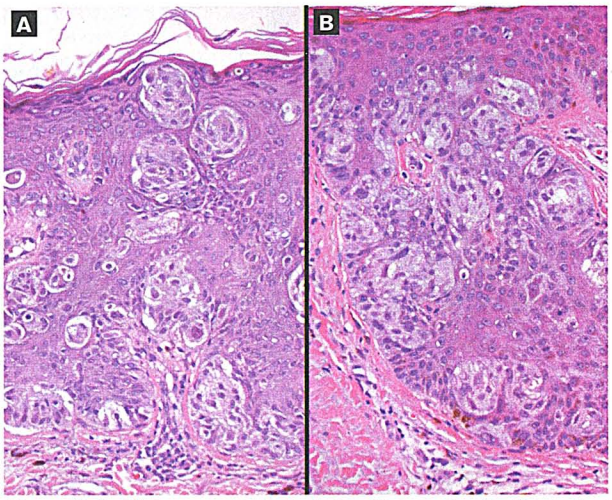

*Figure 2. **A:** Melanoma in situ is defined in part by single atypical melanocytes, nests, and migration of melanocytes above the basal zone (pagetoid spread). **B:** Feature of melanoma is extension of the atypical cells down adnexal structures.*

Melanoma is a malignancy of melanocytes that show a series of molecular events that result in the melanocytes going through a stepwise progression from dysplasia to invasion to metastasis. Melanomas account for approximately 4.4% of all malignancies. Approximately 62,000 new cases of melanoma are reported annually in the United States, and they are responsible for about 7,900 deaths. The incidence of melanoma worldwide has been increasing steadily.

The vast majority of melanomas develop on sun-exposed areas of the skin (topographic differences exist between the sexes), but acral, ocular, mucosal, and solid organ melanomas are not uncommon. The greatest percentage of mucosal melanomas occur in the head and neck area (~55%, although these are not discussed in this installment of Pathology Clinic). Skin melanoma is more common in whites than blacks (>10:1) and in men than women. It is most common in the middle and later decades of life, although patients of all ages have been affected.

At presentation, patients usually report a new skin growth or a change in the size, shape, or color of an existing "mole." The usual warning signs are expressed in the "ABCD" mnemonic: asymmetry, border irregularity, color change, and a diameter of greater than 6 mm. Risk factors for skin melanoma include a previous diagnosis, a family history, sun sensitivity, excessive sun exposure, fair skin and red hair, an immunosuppressive disease, and certain occupational hazards (e.g., exposure to arsenic or creosote).

Melanomas arise from melanocytes, which are the melanin-producing cells of the skin. The neoplasm affects the junction of the epidermis and dermis, in which there is a irregular expansion in the number of melanocytes and a disordered architectural arrangement. Histologically, melanomas are usually large lesions that exhibit an irregular silhouette and a lack of symmetry, showing isolated nests and individual cells at the periphery, often extending along the junction for quite a distance (figure 1). Sometimes a residual benign nevus is present, which hinders the pathologist's ability to accurately determine

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CIPRODEX®
(ciprofloxacin 0.3% and dexamethasone 0.1%)
STERILE OTIC SUSPENSION

CIPRODEX® Otic is indicated in patients 6 months and older for acute otitis media with tympanostomy tubes due to *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* and *Pseudomonas aeruginosa*. CIPRODEX® Otic is contraindicated in patients with a history of hypersensitivity to ciprofloxacin, to other quinolones, or to any of the components in this medication. Use of this product is contraindicated in viral infections of the external canal including herpes simplex infections. CIPRODEX® Otic should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic quinolones. Serious acute hypersensitivity reactions may require immediate emergency treatment. If the infection is not improved after one week of treatment, cultures should be obtained to guide further treatment. Most commonly reported adverse reactions in clinical trials in AOM patients with tympanostomy tubes: ear discomfort (3.0%), ear pain (2.3%), ear residue (0.5%), irritability (0.5%) and taste perversion (0.5%).

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STERILE OTIC SUSPENSION

DESCRIPTION
CIPRODEX® (ciprofloxacin 0.3% and dexamethasone 0.1%) Sterile Otic Suspension contains the synthetic broad-spectrum antibacterial agent, ciprofloxacin hydrochloride, combined with the anti-inflammatory corticosteroid, dexamethasone, in a sterile, preserved suspension for otic use. Each mL of CIPRODEX® Otic contains ciprofloxacin hydrochloride (equivalent to 3 mg ciprofloxacin base), 1 mg dexamethasone, and 0.1 mg benzalkonium chloride as a preservative. The inactive ingredients are boric acid, sodium chloride, hydroxyethyl cellulose, tyloxapol, acetic acid, sodium acetate, edetate disodium, and purified water. Sodium hydroxide or hydrochloric acid may be added for adjustment of pH.

Ciprofloxacin, a fluoroquinolone is available as the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. The empirical formula is $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$. Dexamethasone, 9-fluoro-11(beta),17,21-trihydroxy-16(alpha)-methylpregna-1,4-diene-3,20-dione, is an anti-inflammatory corticosteroid. The empirical formula is $C_{22}H_{29}FO_5$.

CLINICAL PHARMACOLOGY
Pharmacokinetics: Following a single bilateral 4-drop (total dose = 0.28 mL, 0.84 mg ciprofloxacin, 0.28 mg dexamethasone) topical otic dose of CIPRODEX® Otic to pediatric patients after tympanostomy tube insertion, measurable plasma concentrations of ciprofloxacin and dexamethasone were observed at 6 hours following administration in 2 of 9 patients and 5 of 9 patients, respectively.

Mean ± SD peak plasma concentrations of ciprofloxacin were 1.39 ± 0.880 ng/mL (n=9). Peak plasma concentrations ranged from 0.543 ng/mL to 3.45 ng/mL and were on average approximately 0.1% of peak plasma concentrations achieved with an oral dose of 250-mg [3]. Peak plasma concentrations of ciprofloxacin were observed within 15 minutes to 2 hours post dose application. Mean ± SD peak plasma concentrations of dexamethasone were 1.14 ± 1.54 ng/mL (n=9). Peak plasma concentrations ranged from 0.135 ng/mL to 5.10 ng/mL and were on average approximately 14% of peak concentrations reported in the literature following an oral 0.5-mg tablet dose[4]. Peak plasma concentrations of dexamethasone were observed within 15 minutes to 2 hours post dose application. Dexamethasone has been added to aid in the resolution of the inflammatory response accompanying bacterial infection (such as otorrhea in pediatric patients with AOM with tympanostomy tubes).

Microbiology: Ciprofloxacin has *in vitro* activity against a wide range of gram-positive and gram-negative microorganisms. The bactericidal action of ciprofloxacin results from interference with the enzyme, DNA gyrase, which is needed for the synthesis of bacterial DNA. Cross-resistance has been observed between ciprofloxacin and other fluoroquinolones. There is generally no cross-resistance between ciprofloxacin and other classes of antibacterial agents such as beta-lactams or aminoglycosides.

Ciprofloxacin has been shown to be active against most isolates of the following microorganisms, both *in vitro* and clinically in otic infections as described in the **INDICATIONS AND USAGE** section.

Aerobic and facultative gram-positive microorganisms: *Staphylococcus aureus, Streptococcus pneumoniae.* **Aerobic and facultative gram-negative microorganisms:** *Haemophilus influenzae, Moraxella catarrhalis, Pseudomonas aeruginosa.*

INDICATIONS AND USAGE: CIPRODEX® Otic is indicated for the treatment of infections caused by susceptible isolates of the designated microorganisms in the specific conditions listed below: **Acute Otitis Media** in pediatric patients (age 6 months and older) with tympanostomy tubes due to *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis,* and *Pseudomonas aeruginosa.* **Acute Otitis Externa** in pediatric (age 6 months and older), adult and elderly patients due to *Staphylococcus aureus* and *Pseudomonas aeruginosa.*

CONTRAINDICATIONS
CIPRODEX® Otic is contraindicated in patients with a history of hypersensitivity to ciprofloxacin, to other quinolones, or to any of the components in this medication. Use of this product is contraindicated in viral infections of the external canal including herpes simplex infections.

WARNINGS
FOR OTIC USE ONLY (This product is not approved for ophthalmic use.) **NOT FOR INJECTION**

CIPRODEX® Otic should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic quinolones. Serious acute hypersensitivity reactions may require immediate emergency treatment.

PRECAUTIONS
General: As with other antibacterial preparations, use of this product may result in overgrowth of nonsusceptible organisms, including yeast and fungi. If the infection is not improved after one week of treatment, cultures should be obtained to guide further treatment. If otorrhea persists after a full course of therapy, or if two or more episodes of otorrhea occur within six months, further evaluation is recommended to exclude an underlying condition such as cholesteatoma, foreign body, or a tumor. The systemic administration of quinolones, including ciprofloxacin at doses much higher than given or absorbed by the otic route, has led to lesions or erosions of the cartilage in weight-bearing joints and other signs of arthropathy in immature animals of various species. Guinea pigs dosed in the middle ear with CIPRODEX® Otic for one month exhibited no drug-related structural or functional changes of the cochlear hair cells and no lesions in the ossicles. CIPRODEX® Otic was also shown to lack dermal sensitizing potential in the guinea pig when tested according to the method of Buehler. No signs of local irritation were found when CIPRODEX® Otic was applied topically in the rabbit eye. **Information for Patients:** For otic use only. (This product is not approved for use in the eye.) Warm the bottle in your hand for one to two minutes prior to use and shake well immediately before using. Avoid contaminating the tip with material from the ear, fingers, or other sources. Protect from light. If rash or allergic reaction occurs, discontinue use immediately and contact your physician. It is very important to use the ear drops for as long as the doctor has instructed, **even if the symptoms improve**. Discard unused portion after therapy is completed. **Acute Otitis Media in pediatric patients with tympanostomy tubes:** Prior to administration of CIPRODEX® Otic in patients (6 months and older) with acute otitis media through tympanostomy tubes, the solution should be warmed by holding the bottle in the hand for one or two minutes to avoid dizziness which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the drops should be instilled. The tragus should then be pumped 5 times by pushing inward to facilitate penetration of the drops into the middle ear. This position should be maintained for 60 seconds. Repeat, if necessary, for the opposite ear (see **DOSAGE AND ADMINISTRATION**). **Acute Otitis Externa:** Prior to administration of CIPRODEX® Otic in patients with acute otitis externa, the solution should be warmed by holding the bottle in the hand for one or two minutes to avoid dizziness which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the drops should be instilled. This position should be maintained for 60 seconds to facilitate penetration of the drops into the ear canal. Repeat, if necessary, for the opposite ear (see **DOSAGE AND ADMINISTRATION**).

Drug Interactions: Specific drug interaction studies have not been conducted with CIPRODEX® Otic. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term carcinogenicity studies in mice and rats have been completed for ciprofloxacin. After daily oral doses of 750 mg/kg (mice) and 250 mg/kg (rats) were administered for up to 2 years, there was no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species. No long term studies of CIPRODEX® Otic have been performed to evaluate carcinogenic potential. Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin, and the test results are listed below: *Salmonella*/Microsome Test (Negative), *E. coli* DNA Repair Assay (Negative), Mouse Lymphoma Cell Forward Mutation Assay (Positive), Chinese Hamster V79 Cell HGPRT Test (Negative), Syrian Hamster Embryo Cell Transformation Assay (Negative), *Saccharomyces cerevisiae* Point Mutation Assay (Negative), *Saccharomyces cerevisiae* Mitotic Crossover and Gene Conversion Assay (Negative), Rat Hepatocyte DNA Repair Assay (Positive). Thus, 2 of the 8 tests were positive, but results of the following 3 *in vivo* test systems gave negative results: Rat Hepatocyte DNA Repair Assay, Micronucleus Test (Mice), Dominant Lethal Test (Mice). Fertility studies performed in rats at oral doses of ciprofloxacin up to 100 mg/kg/day revealed no evidence of impairment. This would be over 100 times the maximum recommended clinical dose of ototopical ciprofloxacin based upon body surface area, assuming total absorption of ciprofloxacin from the ear of a patient treated with CIPRODEX® Otic twice per day according to label directions. Long term studies have not been performed to evaluate the carcinogenic potential of topical otic dexamethasone. Dexamethasone has been tested for *in vitro* and *in vivo* genotoxic potential and shown to be positive in the following assays: chromosomal aberrations, sister-chromatid exchange in human lymphocytes and micronuclei and sister-chromatid exchanges in mouse bone marrow. However, the Ames/Salmonella assay, both with and without S9 mix, did not show any increase in His+ revertants. The effect of dexamethasone on fertility has not been investigated following topical otic application. However, the lowest toxic dose of dexamethasone identified following topical dermal application was 1.802 mg/kg in a 26-week study in male rats and resulted in changes to the testes, epididymis, sperm duct, prostate, seminal vessicle, Cowper's gland and accessory glands. The relevance of this study for short term topical otic use is unknown.

Pregnancy

Teratogenic Effects. Pregnancy Category C: Reproduction studies have been performed in rats and mice using oral doses of up to 100 mg/kg and IV doses up to 30 mg/kg and have revealed no evidence of harm to the fetus as a result of ciprofloxacin. In rabbits, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose. After intravenous administration of doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit, and no embryotoxicity or teratogenicity was observed. Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. Animal reproduction studies have not been conducted with CIPRODEX® Otic. No adequate and well controlled studies have been performed in pregnant women. Caution should be exercised when CIPRODEX® Otic is used by a pregnant woman.

Nursing Mothers: Ciprofloxacin and corticosteroids, as a class, appear in milk following oral administration. Dexamethasone in breast milk could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical otic administration of ciprofloxacin or dexamethasone could result in sufficient systemic absorption to produce detectable quantities in human milk. Because of the potential for unwanted effects in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and efficacy of CIPRODEX® Otic have been established in pediatric patients 6 months and older (937 patients) in adequate and well-controlled clinical trials. Although no data are available on patients less than age 6 months, there are no known safety concerns or differences in the disease process in this population that would preclude use of this product. (See **DOSAGE AND ADMINISTRATION**.) No clinically relevant changes in hearing function were observed in 69 pediatric patients (age 4 to 12 years) treated with CIPRODEX® Otic and tested for audiometric parameters.

ADVERSE REACTIONS
In Phases II and III clinical trials, a total of 937 patients were treated with CIPRODEX® Otic. This included 400 patients with acute otitis media with tympanostomy tubes and 537 patients with acute otitis externa. The reported treatment-related adverse events are listed below:

Acute Otitis Media in pediatric patients with tympanostomy tubes: The following treatment-related adverse events occurred in 0.5% or more of the patients with non-intact tympanic membranes.

Adverse Event	Incidence (N=400)
Ear discomfort	3.0%
Ear pain	2.3%
Ear precipitate (residue)	0.5%
Irritability	0.5%
Taste perversion	0.5%

The following treatment-related adverse events were each reported in a single patient: tympanostomy tube blockage; ear pruritus; tinnitus; oral moniliasis; crying; dizziness; and erythema. **Acute Otitis Externa:** The following treatment-related adverse events occurred in 0.4% or more of the patients with intact tympanic membranes.

Adverse Event	Incidence (N=537)
Ear pruritus	1.5%
Ear debris	0.6%
Superimposed ear infection	0.6%
Ear congestion	0.4%
Ear pain	0.4%
Erythema	0.4%

The following treatment-related adverse events were each reported in a single patient: ear discomfort; decreased hearing; and ear disorder (tingling).

DOSAGE AND ADMINISTRATION
CIPRODEX® OTIC SHOULD BE SHAKEN WELL IMMEDIATELY BEFORE USE

CIPRODEX® Otic contains 3 mg/mL (3000 µg/mL) ciprofloxacin and 1 mg/mL dexamethasone.

Acute Otitis Media in pediatric patients with tympanostomy tubes: The recommended dosage regimen for the treatment of acute otitis media in pediatric patients (age 6 months and older) through tympanostomy tubes is: Four drops (0.14 mL, 0.42 mg ciprofloxacin, 0.14 mg dexamethasone) instilled into the affected ear twice daily for seven days. The solution should be warmed by holding the bottle in the hand for one or two minutes to avoid dizziness, which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the drops should be instilled. The tragus should then be pumped 5 times by pushing inward to facilitate penetration of the drops into the middle ear. This position should be maintained for 60 seconds. Repeat, if necessary, for the opposite ear. Discard unused portion after therapy is completed. **Acute Otitis Externa:** The recommended dosage regimen for the treatment of acute otitis externa is: For patients (age 6 months and older): Four drops (0.14 mL, 0.42 mg ciprofloxacin, 0.14 mg dexamethasone) instilled into the affected ear twice daily for seven days. The solution should be warmed by holding the bottle in the hand for one or two minutes to avoid dizziness, which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the drops should be instilled. This position should be maintained for 60 seconds to facilitate penetration of the drops into the ear canal. Repeat, if necessary, for the opposite ear. Discard unused portion after therapy is completed.

HOW SUPPLIED
CIPRODEX® (ciprofloxacin 0.3% and dexamethasone 0.1%) Sterile Otic Suspension is supplied as follows: 5 mL fill and 7.5 mL fill in a DROP-TAINER® system. The DROP-TAINER® system consists of a natural polyethylene bottle and natural plug, with a white polypropylene closure. Tamper evidence is provided with a shrink band around the closure and neck area of the package. NDC 0065-8533-01, 5 mL fill; NDC 0065-8533-02, 7.5 mL fill. **Storage:** Store at controlled room temperature, 15°C to 30°C (59°F to 86°F). Avoid freezing. Protect from light.

Clinical Studies: In a randomized, multicenter, controlled clinical trial, CIPRODEX® Otic dosed 2 times per day for 7 days demonstrated clinical cures in the per protocol analysis in 86% of AOMT patients compared to 79% for ofloxacin solution, 0.3%, dosed 2 times per day for 10 days. Among culture positive patients, clinical cures were 90% for CIPRODEX® Otic compared to 79% for ofloxacin solution, 0.3%. Microbiological eradication rates for these patients in the same clinical trial were 91% for CIPRODEX® Otic compared to 82% for ofloxacin solution, 0.3%. In 2 randomized multicenter, controlled clinical trials, CIPRODEX® Otic dosed 2 times per day for 7 days demonstrated clinical cures in 87% and 94% of per protocol evaluable AOE patients, respectively, compared to 84% and 89%, respectively, for otic suspension containing neomycin 0.35%, polymyxin B 10,000 IU/mL, and hydrocortisone 1.0% (neo/poly/HC). Among culture positive patients clinical cures were 86% and 92% for CIPRODEX® Otic compared to 84% and 89%, respectively, for neo/poly/HC. Microbiological eradication rates for these patients in the same clinical trials were 86% and 92% for CIPRODEX® Otic compared to 85% and 85%, respectively, for neo/poly/HC.

References:

1. CIPRODEX® Otic package insert.
2. Wolters Kluwer Health, Source® Pharmaceutical Audit Suite, April 2006 - March 2007. Based on total monthly prescription counts.
3. Campoli-Richards DM, Monk JP, Price A, Benfield P, Todd PA, Ward A. Ciprofloxacin: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs.* 1988;35:373-447.
4. Loew D, Schuster O, Graul E. Dose-dependent pharmacokinetics of dexamethasone. *Eur J Clin Pharmacol.* 1986;30:225-230.

U.S. Patent Nos. 4,844,902; 6,284,804; 6,359,016

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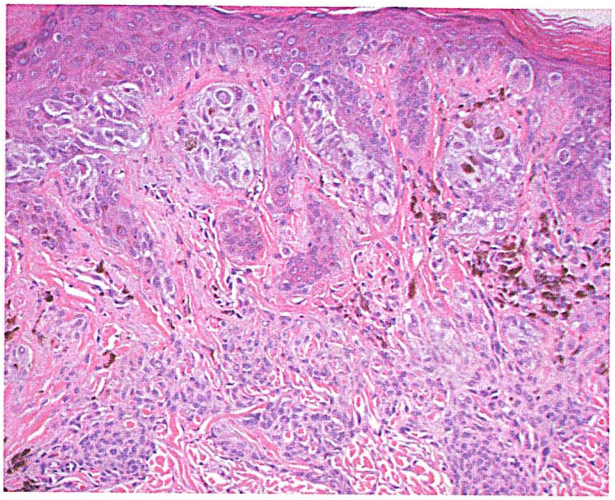

Figure 3. The typical melanocytes are associated with desmoplastic stroma in the dermis. Pigment is present, and cellular pleomorphism is noted.

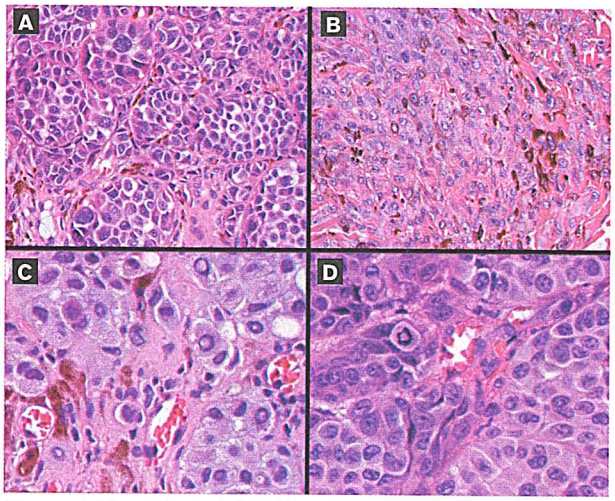

*Figure 4. These images show a number of features seen in melanoma, including nuclear pleomorphism (**A**), desmoplastic stroma with intracellular pigmentation (**B**), intranuclear cytoplasmic inclusions (**C**), and increased mitotic figures (**D**).*

where the melanoma ends and the nevus begins. Several prognostic histologic features may be present, including surface ulceration, an inflammatory infiltrate at the advancing dermal border, desmoplastic fibrosis, regression (i.e., fibrosis, granulation-tissue–type vessels, and pigment-laden histiocytes), and vascular invasion. Compared with benign nevi, melanoma is more likely to be associated with a confluence of atypical single cells, nests of various sizes and shapes, and migration of the melanocytes above the basal zone into the upper layers of the epidermis or extension down adnexal structures (pagetoid spread) (figure 2).

The melanocytes invade into the dermis (vertical-growth phase) in a variety of architectural patterns, including nested, fascicular, solid, organoid, storiform, peritheliomatous, and papillary, to name just a few (figure 3). Pigment may be present within the tumor cells or picked up by macrophages in the stroma, although amelanotic melanomas are seen. Mitotic figures, including atypical forms, are usually easy to find. The neoplastic cells are protean, ranging from small cells with a high nucleus-to-cytoplasm ratio to remarkably pleomorphic cells with abundant cytoplasm. The cells can be undifferentiated, epithelioid, spindled, plasmacytoid, rhabdoid, giant-cell, or polygonal. The nuclei contain dense, coarse nuclear chromatin and prominent, irregular eosinophilic nucleoli; they frequently show intranuclear cytoplasmic inclusions (figure 4).

Breslow's depth of invasion (measured in hundredths of a millimeter) and *Clark's level of invasion* into the layers of the dermis (papillary dermis, reticular dermis, and subcutaneous layer) are both important components of the diagnosis, as they guide therapy and yield prognostic information. Immunohistochemistry stains (S-100 protein, HMB-45, melan-A, and tyrosinase) can help confirm the melanocytic nature of the tumor, but the histologic features of malignancy must be present to make the diagnosis of melanoma. The term *melanoma in situ* is used when the basement membrane of the epidermis is not penetrated by the melanocytes (about 50,000 such cases occur yearly in the U.S.). Needless to say, there are several patterns and histologic subtypes that are clinically important (e.g., desmoplastic melanoma, nevoid melanoma, and spindle-cell melanoma).

Most melanomas (>80%) are detected early (in situ disease or limited depth of invasion), and the prospects for long-term survival are excellent (5-yr survival: 98%). However, if regional disease (metastasis to the local lymph nodes) develops, survival decreases (5-yr survival: 64%). The prognosis is much worse in cases of distant metastasis (5-yr survival: 16%).

Prompt surgical excision, including a margin of uninvolved skin, followed by a sampling of the draining lymph nodes (sentinel lymph node) for staging, is the initial mainstay of therapy. Advanced disease is managed with multimodal therapy, but results have been mixed. Early detection by regular skin examinations and microscopic examination of all suspicious lesions is essential.

Suggested reading

Markovic SN, Erickson LA, Rao RD, et al. Malignant melanoma in the 21st century, part 1: Epidemiology, risk factors, screening, prevention, and diagnosis. Mayo Clin Proc 2007;82(3):364-80.

Markovic SN, Erickson LA, Rao RD, et al. Malignant melanoma in the 21st century, part 2: Staging, prognosis, and treatment. Mayo Clin Proc 2007;82(4):490-513.

Miller AJ, Mimh MC Jr. Melanoma. N Engl J Med 2006:355(1):51-65.