Both fibrillin molecules and fibrillin-rich microfibrils are susceptible to degradation by serine proteases, and the amino acid substitutions found in Marfan syndrome change the fragmentation patterns. Fibrillin degradation products generated by MMP activity provide conclusive evidence that these enzymes cause specific changes to assembled microfibrils. In Marfan syndrome, most of the mutations in fibrillin-1 are found within epidermal growth factor–like motifs and are predicted to disrupt calcium binding. These mutations may render fibrillin-1 more susceptible to proteolytic cleavage. Patients with isolated ectopia lentis may also have an increased susceptibility to zonular degradation. Structural modifications in fibrillin-rich microfibrils occur during aging of the human ciliary zonule. These age-related changes may account for the increased incidence of ocular disease in older patients with ectopia lentis. The hypothesis regarding the role of MMPs in lens subluxation implies that an imbalance of lens proteases and their antagonists may be involved in the development of ectopia lentis.

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Orbital Metastasis and Intraocular Invasion of Malignant Mixed Tumor (Carcinosarcoma) of the Parotid Gland in a Child

Malignant mixed tumor of the salivary glands is a rare neoplasm, and the majority of these tumors arise from the parotid gland. Histopathologically, 3 distinct variants of malignant mixed tumors are recognized, the most common being carcinoma arising from a preexisting pleomorphic adenoma. The second type is the metastasizing mixed tumor, which has benign-appearing epithelial and stromal components. The true malignant mixed tumor or carcinosarcoma, an exceptionally rare tumor, is the third subtype and is composed of malignant epithelial and malignant mesenchymal elements.

Less than 5% of all salivary gland neoplasms are seen in patients younger than 16 years and 13% of these tumors are solid, of which only 23% are malignant. The most common malignant salivary gland tumor in children is mucoepidermoid carcinoma, followed by rhabdomyosarcoma and acinic cell carcinoma. We herein describe a highly unusual patient with a carcinosarcoma of the parotid gland that metastasized to ipsilateral orbit and intraocular structures.

Report of a Case. A 10-year-old boy was seen at another institution because of right orbital and preauricular masses that evolved gradually during a period of 6 months (Figure 1). His medical history included trabeculectomy for right congenital glaucoma at the age of 3 years. His records indicate that there was no evidence of an intraocular mass or iris neovascularization.

Visual acuity in the right eye had remained no light perception since then. Magnetic resonance images showed a right anterior orbital and preseptal mass, as well as a large

Figure 1. Patient at initial examination, the day after the incisional biopsy was performed.
noncystic tumor occupying the right anterior superficial part of the parotid gland (Figure 2). After an unsuccessful trial of systemic antibiotics for 10 days, an incisional biopsy specimen obtained through the superior lid crease was reported as showing alveolar rhabdomyosarcoma. A fine-needle aspiration biopsy specimen from the parotid mass showed round-cell malignant tumor, which was interpreted as metastatic rhabdomyosarcoma.

The patient received 14 cycles of vincristine sulfate, 1.5 mg/m²; etoposide, 150 mg/m²; ifosfamide, 2 mg/m²; and doxorubicin hydrochloride, 20 mg/m². The right orbit and the parotid gland region were irradiated with a total dose of 5400 rad (54 Gy) by 200-rad (2-Gy) fractions. Because there was only partial response to this treatment, the patient was referred to our center.

On our examination, the right eye had no light perception and the visual acuity in the left eye was 20/20. On the right side, there was a single large episcleral mass that was fleshy, red, immobile, painless, and hard on palpation (Figure 3). The cornea was opaque, and no fundus details could be seen. Ultrasonography failed to detect a definable intraocular solid lesion. The left eye was normal. A systemic workup failed to show any distant metastases.

A total right parotidectomy and enucleation of the right eye including the episcleral nodule were performed. Histopathologic examinations showed carcinosarcoma of the

Figure 2. T1-weighted axial magnetic resonance images. A, The anterior orbital mass is homogeneously hypointense relative to the orbital fat. B, A large, homogeneous solid mass arises from the right anterior superficial part of the parotid gland.

Figure 3. Lack of total regression of the epibulbar and preauricular tumors 15 months later, despite radiotherapy and intensive chemotherapy.

Figure 4. Gross view of the parotid gland showing the cut surface. The tumor measured 7 × 5.5 × 3.5 cm. There was no intratumoral hemorrhage or necrosis despite previous treatment.

Figure 5. Gross view of the enucleated eye showing the large episcleral metastatic tumor and the trabeculectomy site (arrow) through which the tumor presumably invaded the intraocular compartment.
The excised parotid gland was firm and had nodular contours, and the cut surfaces were partly tan or creamy white (Figure 4). The globe was small and soft with a firmly adherent superior episcleral nodule (Figure 5). There were scleral thickening and posterior staphyloma formation. The site of trabeculectomy through which neoplastic tissues extended into the globe was easily identified. On light microscopy, the tumor was composed of columns of epithelial cells forming adnexoid structures and islands of hypercellular cartilage (Figure 6). There were atypical chondroid cells showing pleomorphism, and the lacunae contained more than 1 nucleus, suggesting malignancy (Figure 7). Residual islands of normal parotid gland tissues were also observed. The intraocular tumor was also composed of mixed malignant chondroid and epithelial elements (Figure 8). There was no evidence of uveal tract involvement. The results of immunohistochemical and histochemical studies are shown in Table 1 and Table 2, respectively. The chondroid and epithelial cells contained abundant glycogen, and the luminal surface of epithelial cells had neutral mucin. Almost identical features were observed on reevaluation of the slides of the initial incisional biopsy, erroneously reported as rhabdomyosarcoma.

Comment. This patient underwent a series of extremely unusual events, including parotid gland malignancy with the exceptionally rare form of de novo carcinosarcoma at the age of 10 years and metastases to the orbit and episcleral tissues, with intraocular invasion through a trabeculectomy site. Patients with malignant mixed tumor of the parotid gland usually have onset in the fifth decade of life (range, 7-86 years), with a history of a mass of 10 to 50 years’ duration. Carcinosarcoma comprises only 0.4% of all sali-
vary gland tumors, and, by definition, both epithelial and mesenchymal components should fulfill the criteria for malignancy and typically metastasize together.3,6 Criteria for malignancy include destruction of normal tissues, invasiveness, cellular anaplasia, pleomorphism, and atypical mitoses.2 A high-grade ductal carcinoma is the usual epithelial component, whereas chondrosarcoma is the most common mesenchymal component.2 However, fibrosarcoma, leiomyosarcoma, osteosarcoma, and rhabdomyosarcoma may also be encountered.3,7 Our patient clearly showed definable carcinomatous and sarcomatous areas in the primary and metastatic tumors. Carcinosarcoma may also develop years after irradiation of a pleomorphic adenoma.2,3 Our case probably represents carcinosarcoma arising de novo, which is another rarity in itself.

Controversy surrounds the cell of origin of malignant mixed tumor in general and carcinosarcoma in particular. There is recent evidence that myoepithelial cells may serve as a common stem cell for both carcinomatous and sarcomatous components.6 Myoepithelial cells express keratins, vimentin, and S100.9 Tests for smooth-muscle actin and muscle-specific actin may be positive in 50% of cases, whereas tests for carcinoembryonic antigen, which indicates luminal differentiation and epithelial membrane antigen, are typically negative.9 Neoplastic chondrocytes express vimentin and are thought to develop by metaplastic myoepithelial cells.10 Our immunohistochemical staining results support these findings.

Malignant teratoid medulloepithelioma must be considered in the differential diagnosis of our case. This tumor may cause neovascular or angle-closure glaucoma, and histopathologically it may contain undifferentiated neuroblastic cells resembling retinoblastoma and heteroplastic tissues including brain, skeletal muscles, and cartilage.11 Furthermore, criteria for malignancy include uveal invasion and the presence of sarcomatous elements like chondrosarcoma, rhabdomyosarcoma, or embryonal sarcoma, among others.12 However, a carcinomatous component and the presence of both mesenchymal and carcinomatous elements at metastatic sites are not features of malignant teratoid medulloepithelioma, which shows intracranial extension rather than distant metastases in most cases. More than 50% of patients with carcinosarcoma develop metastases, and the most common sites include lungs, liver, bones, local and hilar lymph nodes, and central nervous system.3,7 To the best of our knowledge, orbit and intraocular structures have not been previously reported as metastatic sites. This unique case, therefore, represents a collection of exceptionally rare events and demonstrates that

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<th>Table 1. Results of Immunohistochemical Staining</th>
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<td>Antigen</td>
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<tr>
<td>Pan-CK</td>
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<td>Keratin 8-18</td>
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<td>CEA</td>
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<td>α-Lactalbumin</td>
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Abbreviations: CEA, carcinoembryonic antigen; CK, cytokeratin; EMA, epithelial membrane antigen; GFAP, glial fibrillary acidic protein; SMA, smooth-muscle actin; +, positive staining; −, negative staining.

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<th>Table 2. Results of Histochemical Staining</th>
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<td>Stain</td>
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<td>--------------------------------------------</td>
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<tr>
<td>Diastase and PAS</td>
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<tr>
<td>d-PAS and Alcian blue (pH 2.5)</td>
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<td>Alcian blue (pH 2.5) and hyaluronidase</td>
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<td>Alcian blue (pH 0.5) and hyaluronidase</td>
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<td>Mucicarmine</td>
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Abbreviations: d-PAS, diastase–periodic acid–Schiff; +, positive staining; −, negative staining.
carcinosarcoma may occur in children and metastasize regionally as well.

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Primary orbital melanoma is an exceedingly rare tumor that probably develops from congenital rests of neural crest cells in the orbit. It represents less than 1% of primary orbital neoplasms and usually occurs in the presence of clinical or histological evidence of ocular melanosis or blue nevus syndrome. Although orbital melanoma in general carries a poor prognosis, our case was unusual for its extremely aggressive clinical course that resulted in the death of the patient 6 months after presentation.

Report of a Case. A 40-year-old white man was first seen by us in July 1998 with a painless 3-mm proptosis of the left eye of 6 months’ duration. There was no clinical evidence of ocular melanosis or blue nevus syndrome. A computed tomographic scan of the orbits revealed a well-defined intraconal mass that was discrete from the optic nerve and the horizontal rectus muscles (Figure 1). In the following 6 weeks, the proptosis enlarged, progressing from 3 mm to 8 mm. There was associated conjunctival exposure with ulceration, marked global restriction of movement, and transient visual obscurations. Optic nerve function was preserved, with Snellen visual acuity retained at 6/5, normal color vision, and intact pupillary reactions. A lateral orbitotomy with excision biopsy was performed in September 1998. A large pigmented mass was removed, histological analysis of which showed the lesion to be an orbital melanoma. A cilioretinal artery occlusion occurred postoperatively, reducing the left visual acuity to light perception.

Histologically, it is not possible to differentiate a primary from a metastatic orbital melanoma; therefore, we performed a thorough systemic evaluation for a primary source. Detailed clinical examination augmented with liver function tests; liver ultrasonography; computed tomographic imaging of the brain, chest, and abdomen; and a bone scan showed no evidence of systemic melanoma. Ocular B-scan ultrasonography, performed to look for an intraocular primary tumor, suggested a possible small anterior ciliary body lesion with a collar-stud appearance and measuring 1.4 mm.

Five weeks after the excision biopsy, there was an alarmingly rapid recurrence of the left proptosis (Figure 2 and Figure 3). Magnetic resonance imaging revealed local tumor regrowth occupying the inferior aspect of the left orbit and extending superiorly as far as the superior rectus muscle. There was no evidence of spread beyond the orbit. A left exenteration with preservation of the eyelids was carried out in November 1998. Postoperative radiotherapy, to be followed by chemotherapy and adjunctive interferon therapy, is of considerable interest in this article.

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