Metastatic tumors of the orbit and ocular adnexa

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Purpose of review

The management of cancer metastatic to the orbit and ocular adnexa (eyelid and periocular structures) has changed in recent decades. The purpose of this article is to review the incidence, presentation, and clinical features of metastatic tumors of the orbit and ocular adnexa and discuss their multidisciplinary care.

Recent findings

The improved survival of patients with common cancers such as breast cancer and prostate cancer, together with aging of the population has led to a higher incidence of patients living with metastatic disease in unusual sites such as the orbit and ocular adnexa. Furthermore, vigilant surveillance and advances in diagnostics have led to increased detection of orbital metastases. Treatment of metastatic lesions in the orbit and ocular adnexa is usually palliative and may include radiotherapy, chemotherapy, hormonal therapy, surgery, or a combination of these modalities.

Summary

Breast carcinoma continues to account for the majority of metastatic lesions of the orbit and ocular adnexa. Although the overall prognosis for patients with such lesions remains poor, the longer survival time for patients with breast carcinoma, the availability of novel targeted treatment options and new investigational agents, and advances in radiotherapy techniques may lead to better quality of life and preservation of ocular function for patients with metastatic orbital tumors.

Keywords

breast cancer, eyelid metastasis, lung cancer, orbital metastases, prostate cancer, radiotherapy

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Abbreviation

CT computed tomography

1040-8738

Introduction

Since Horner's initial description in 1864 of a lung cancer metastasis in the orbit, multiple cases of orbital metastases have been described in the literature. A metastasis to the orbit and ocular adnexa (eyelid and periocular structures), however, is rare and occurs less frequently than a metastasis to the eye (uveal metastasis) [1]. As the longevity of cancer patients' has increased, so has the frequency with which these lesions are detected [2–4]. The presence of an orbital or ocular adnexal metastatic lesion usually reflects widespread hematogenous spread of the primary cancer and, with a few exceptions, carries a poor prognosis. The management of metastatic tumors of the orbit and ocular adnexa has changed in recent decades because of the availability of novel targeted systemic treatments and advances in radiotherapy techniques. We herein review the incidence, presentation, clinical features, and diagnosis of metastatic tumors of the orbit and ocular adnexa and discuss the current multidisciplinary care of patients with cancer metastatic to the orbit and ocular adnexa.

Incidence

Metastatic orbital lesions have been estimated to account for 1–13% of all orbital tumors reported [2–13]. The prevalence of orbital metastasis in cancer patients is estimated to range from 2 to 4.7%. The reported incidence of metastatic tumors of the orbit and ocular adnexa has been increasing in recent years. A number of factors may account for this increase. First, improved treatment has led to an increase in the median survival of cancer patients, which in turn increases the chances for development of metastatic lesions in unusual sites such as the orbit and ocular adnexa. Second, advances in diagnostic imaging, increased use of fine-needle aspiration biopsy, and application of serologic and molecular diagnostic imaging techniques have led to increased detection of such lesions [2–5]. Third, an increased volume of medical literature on orbital and ocular adnexal metastases has increased awareness of these lesions across all subspecialties and led to more vigilant surveillance for recurrences.

The true incidence of metastatic tumors of the orbit and ocular adnexa is likely to be higher than suggested in the literature. Several factors may cause underestimation of the true incidence. Patients with small orbital lesions may remain asymptomatic and are less likely to be diagnosed than patients with similarly sized ocular lesions [6]. For example, subclinical metastatic orbital lesions are

estimated to be present in 10–30% of breast cancer patients [2–4,8]. In patients with disseminated disease, orbital symptoms may be overshadowed by general debility leading to a low rate of referral to ophthalmologists. Another factor suggesting that the true incidence may be underestimated is that rates of orbital evaluation at autopsy are low [7].

Anatomical considerations

From the literature, it is difficult to ascertain clearly whether metastatic disease in the orbit is more common on one side than the other. Some studies [10,11] have indicated that metastatic disease is more common in the left orbit. Theoretically, because the left common carotid ascends directly off the aorta, tumor cells from the systemic circulation could have a more direct path to the left orbit. Conversely, other studies [3,8,12] have shown no greater prevalence of metastasis to the left orbit. An analysis [3] of several studies showed that right-sided metastases were more common; this was not, however, statistically significant. Although there are several case reports in the literature of bilateral orbital or ocular adnexal metastases, bilateral disease is a highly unusual presentation.

Although some earlier reviews reported that metastatic lesions were distributed fairly equally in the different quadrants of the orbit, more recent cumulative data [3,12] have shown the following distribution of involvement: lateral quadrant, 39%; superior, 32%; medial, 20%; and inferior, 12%. Another report [8] found that the main component of the metastatic lesion lay in the anterior orbit (posterior sclera to eyelids) in 41 cases and in the posterior orbit (posterior sclera to orbital apex) in 27 cases.

Although different tumor types have a propensity to metastasize to certain tissues [e.g. prostate to bone (Fig. 1), melanoma to extraocular muscles (Fig. 2), and breast to fatty tissue and extraocular muscle], the overall distribution of metastases within the orbit seems to be in a 2:2:1 bone–fat–muscle ratio [3].

Isolated metastases to the eyelid and periocular skin are less common and have been reported mainly in single case reports, most describing cutaneous melanoma nodules [14,15] in the eyelid (Fig. 3) or eyelid metastases in the background of widespread metastatic disease (Fig. 4) [16].

Presentation and clinical features

Orbital metastasis is predominantly a condition of adulthood (76% of cancers are diagnosed in persons aged 75 years or older) and usually arises from carcinomas [4]. Orbital metastasis in children is even more rare and is more likely to arise from sarcomas or embryonal tumors of neural origin. Most orbital and ocular adnexal metastases present in patients with an established diagnosis of cancer and widespread systemic involvement. In 19–25% of cases, there may be no history of cancer, and thus the ophthalmologist may play a crucial role in the detection

Figure 1 Computed tomography scan of the orbit demonstrates bony metastasis (metastatic prostate cancer) to the lateral wall of the orbit with thickening and irregular appearance of the lateral wall

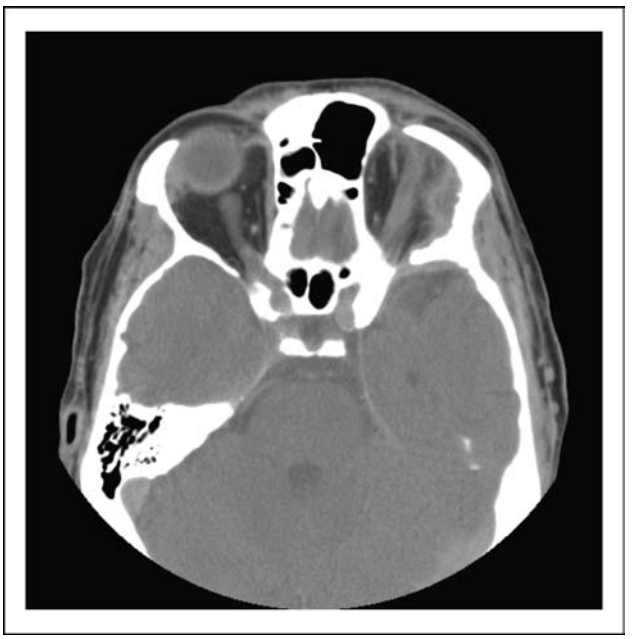


Figure 2 Magnetic resonance image of the orbit demonstrates metastasis to the lateral rectus muscle in a patient with metastatic cutaneous melanoma

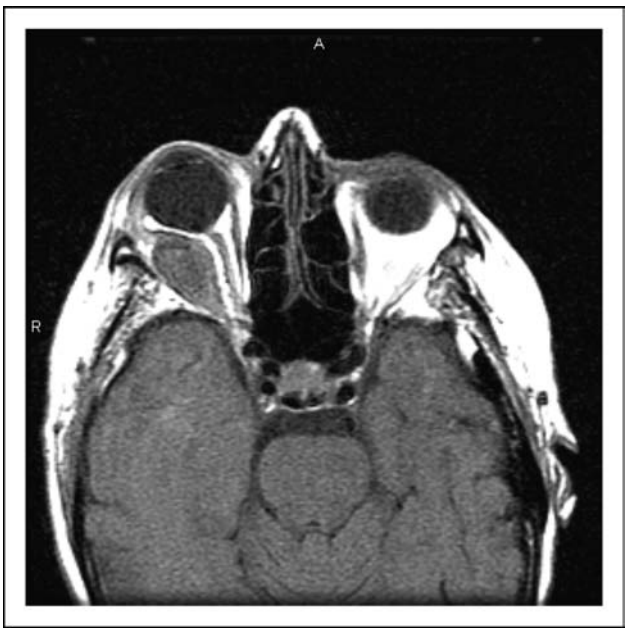
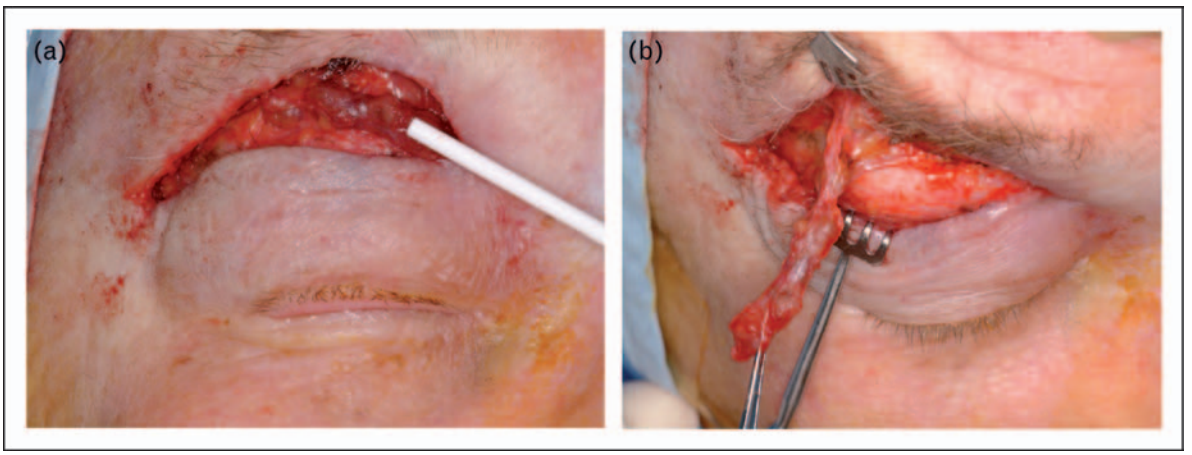


Figure 3 Chain of melanoma nodules



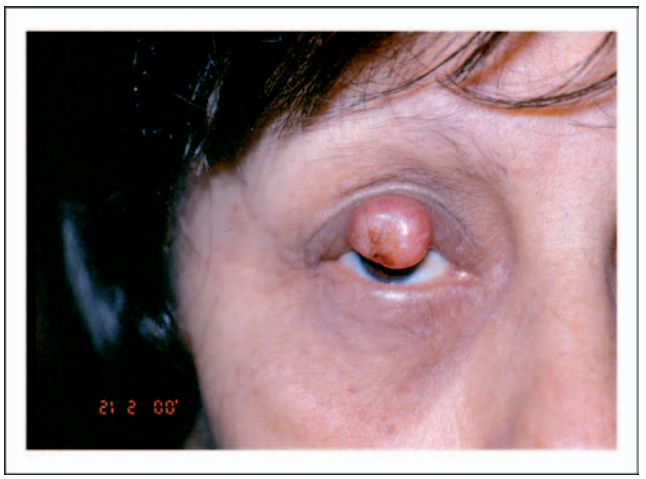
(a) A chain of melanoma nodules in the upper eyelid of a patient with stage IV cutaneous melanoma. (b) The chain of melanoma metastases were removed through an eyelid crease incision.

and staging of a previously unsuspected primary cancer [2–4].

The clinical manifestations of orbital metastasis have been well documented. Generally, there is an unrelenting, rapid onset of symptoms. These symptoms may be progressive over weeks to months. Presenting symptoms and signs from four reports [5,8,9,12] are listed in Table 1.

Typical manifestations of orbital metastases include mass effect causing displacement or proptosis of the globe, pain, inflammation, bone involvement, chemosis, and eyelid swelling. Infiltration of soft tissue structures can lead to ptosis, diplopia, or enophthalmos (Fig. 5). Motility disturbances may be out of proportion to proptosis.

Figure 4 Isolated eyelid metastasis in a patient with leiomyosarcoma



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Enophthalmos is most commonly seen in sclerotic tumors such as scirrhous breast carcinoma and gastric carcinoma. As the signs and symptoms of orbital metastases are nonspecific and provide no clinical framework for categorization of lesions, Goldberg *et al.* [3,9] suggested categorization into five generalized syndromes of presentation, frequencies of which were as follows: infiltrative (53%); mass (37%); inflammatory (5%); functional (3%); and silent (very rare) [3].

Diagnosis

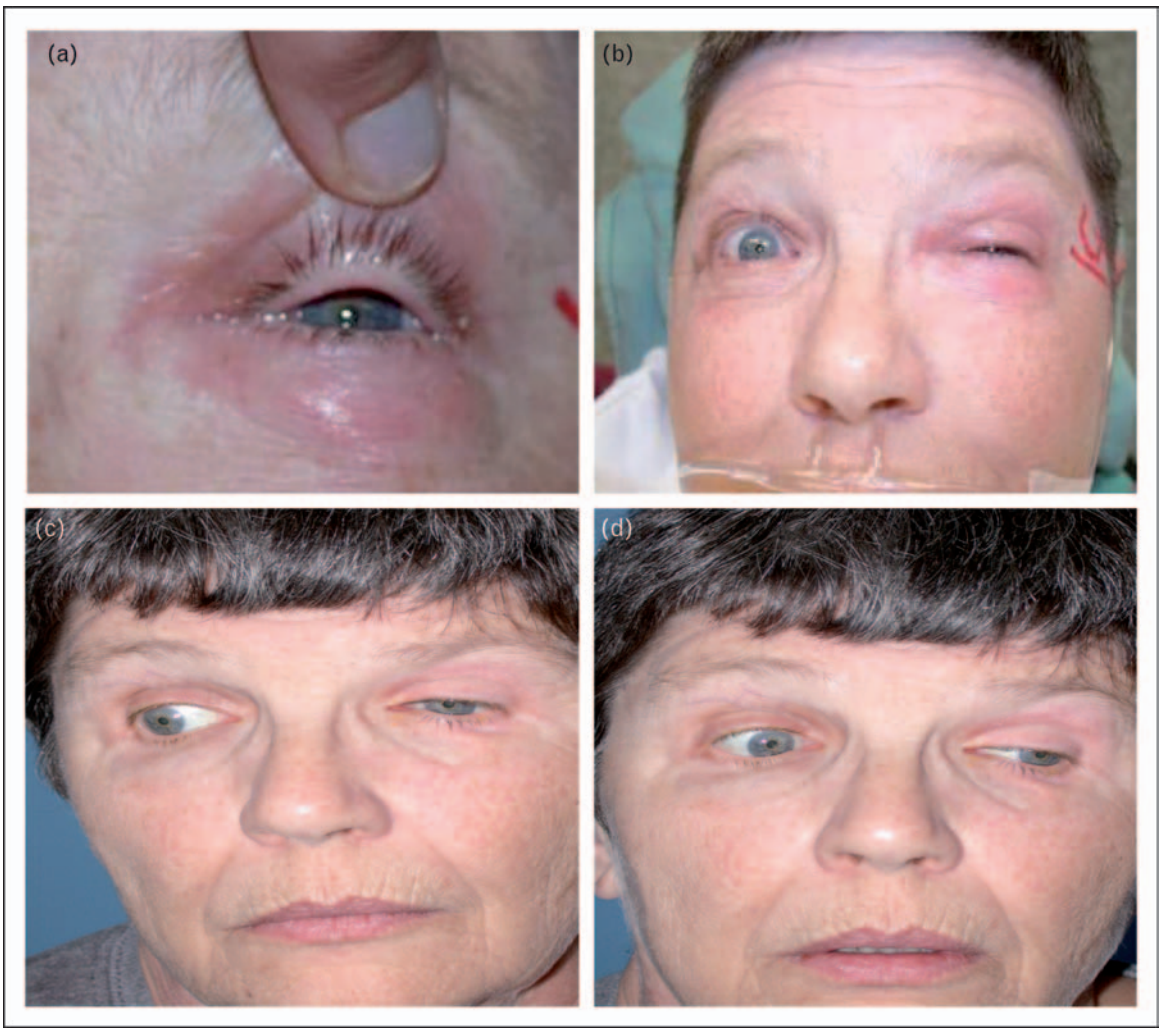
A thorough history, a detailed ophthalmic examination, and general physical assessment are musts in any patient with suspected orbital or ocular adnexal metastasis. In patients with no known history of cancer, prompt referral to an oncologist is necessary so that a simultaneous evaluation for other systemic disease can be initiated.

The differential diagnosis of an orbital tumor can be narrowed to a few possibilities with a meticulous history, examination, and the use of current imaging studies. Computed tomography (CT) and MRI are the principal means of evaluating suspected orbital lesions. Even though CT is usually the first choice in evaluating the orbit, MRI provides the best resolution of orbital soft tissues. CT may be more appropriate in patients with

Table 1 Presenting signs and symptoms in four series of patients with orbital metastases

Sign or symptom	Char [5]	Shields [8]	Goldberg [9]	Font [12]
Diplopia	48%	9%	38%	18%
Proptosis	26%	50%	35%	75%
Decreased vision	16%	23%	20%	29%
Pain	19%	17%	23%	29%
Ptosis	10%	49%	16%	7%
Mass	NA	43%	13%	21%

Figure 5 Patient with breast carcinoma metastatic to the left orbit and periorbital tissues



(a) Photograph of a patient with breast carcinoma metastatic to the left orbit and periorbital tissues. Note the enophthalmos (b) and motility restriction (c,d). In this patient, the eyelid, orbit, and periocular skin were the only detectable sites of metastasis for 5 years before any other sites of metastasis were discovered. The patient has had a long survival after detection of the orbital metastases, the patient had an excellent quality of life and very reasonable visual function; diplopia present only in lateral gaze was her only visual disability.

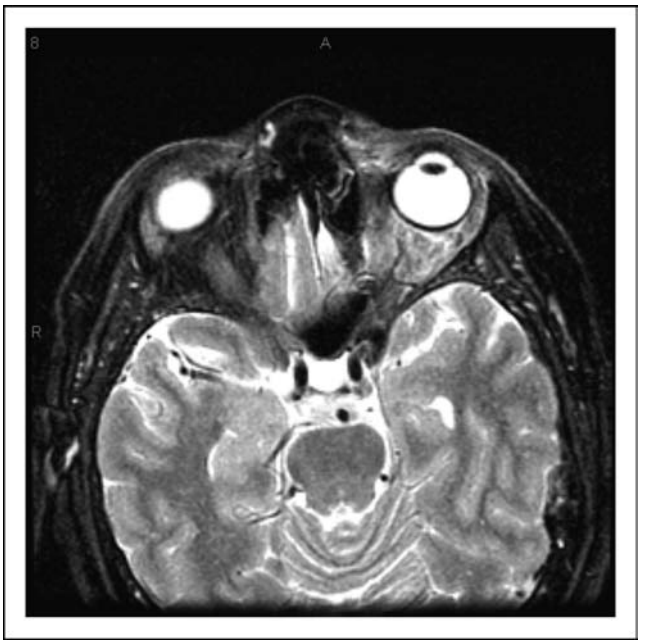
prostate cancer, which has a propensity to metastasize to bone.

Findings on imaging may range from a diffuse infiltrative pattern with obscuration of normal anatomical landmarks to a focal lesion in which a discrete, well defined mass is seen; orbital metastatic lesions can be extraconal (Fig. 6) or intraconal (Fig. 7). Enlargement of one or more of the extraocular muscles may be seen, particularly in patients with metastatic cutaneous melanoma (Fig. 2). Involvement of the bony orbital walls suggests that prostate cancer is the primary tumor. It is unusual to see cystic changes or calcification within metastatic lesions of the orbit.

In patients with widespread metastatic disease and an established diagnosis of cancer, an orbital biopsy can sometimes be forgone and the inherent risks avoided as the diagnosis can be inferred on the basis of the other findings. The potential risks of biopsying a posterior orbital apical mass such as visual loss, bleeding, diplopia, and surgical wound morbidities in an immune compromised cancer patient should always be weighed against the potential benefits, including whether the management options are likely to change as a result of the biopsy.

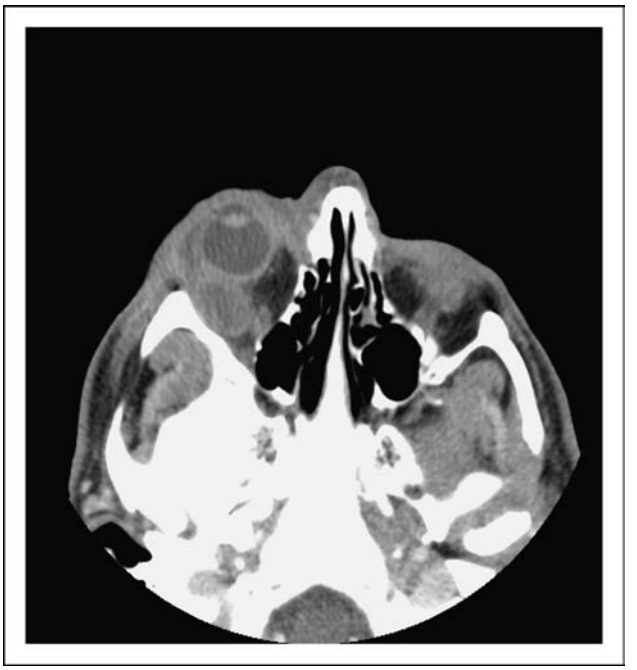
The definitive diagnosis of an orbital lesion requires tissue diagnosis. Fine-needle aspiration biopsy has been advocated by many authorities as an excellent diagnostic modality [3,17–19]. There have, however, been reports [17–19] of dissemination of tumor cells with the procedure, and there is a risk of globe injury, although the likelihood of these complications is low.

Figure 6 Orbital infiltration secondary to metastatic breast cancer



Magnetic resonance image demonstrates orbital infiltration secondary to metastatic breast cancer in the left orbit in the retrobulbar space as well as in the anterior orbital soft tissues and eyelid in the patient shown in Fig. 5.

Figure 7 Computed tomography scan of an intraconal mass in the right orbit, which was histologically proven to be metastatic melanoma



When orbital metastasis is the initial presentation of breast cancer, estrogen receptor expression should be measured in the orbital biopsy specimen, not only to aid in diagnosis but also to determine whether hormonal therapy would be an appropriate treatment. In the Western world, however, with the availability of routine mammography to screen for early stage breast cancer, it is unlikely that the orbital metastatic lesion would be the initial presentation of breast cancer.

Treatment

The aims of treatment for orbital metastases are to maximize the patient's quality of life and restore or preserve visual function. Careful consideration should be given to the patient's general state of health, life expectancy, and the effects of treatment. Treatment for orbital and ocular adnexal metastases is always palliative in the sense that the presence of such metastases suggests hematogenous spread of cancer even if no other sites of hematogenous spread are identifiable.

Treatment may include radiotherapy, chemotherapy, hormonal therapy, or surgery, or some combination of these modalities.

Radiotherapy is the mainstay treatment for orbital and ocular adnexal metastases and is usually administered to control tumor growth, preserve visual function in the short term, decrease proptosis and exposure keratopathy, or to improve patient comfort. The recommended dose is 20–40 Gy delivered in fractions over 1–2 weeks [3–9,20]. Radiotherapy alleviates symptoms in 80% of cases and in some cases restores vision [5]. Cataract formation and radiation retinopathy are potential side effects of external beam radiotherapy; the risk of these side effects is more relevant if the patient is expected to live longer than 1 year. Shielding of the globe may lessen the risk of radiation-induced side effects in some situations [21].

Systemic chemotherapy may be helpful in the treatment of orbital and ocular adnexal metastases, especially from chemosensitive tumors, such as small cell lung cancer and neuroblastoma [22•].

Hormonal therapy plays an important role in the treatment of metastases from hormone-sensitive tumors, such as breast cancer and prostate cancer. It is important that receptor assays be performed on biopsy specimens to establish whether tumors are hormone sensitive.

Generally, orbital surgery to remove the tumor mass is not recommended as this is not curative and may be associated with significant ocular morbidity [2–5,7–9]. In selected cases, however, tumor resection, even if incomplete, may be appropriate to improve the patient's symptoms of pain, diplopia, and disfiguring proptosis and help

restore visual function. This is particularly true for patients with metastatic cutaneous melanoma of the eyelid and periocular skin, in whom total removal of the mass may be possible with relatively low morbidity (Fig. 3). Enucleation or other radical measures offer no advantage in terms of progression or survival and should be used only in cases of intractable ocular pain or unmanageable local hygiene due to rapid tumor growth.

Types of cancer metastatic to the orbit

Any cancer that can spread via the hematogenous route can metastasize to the orbit and ocular adnexal structures. The following are the most common cancer types that metastasize to the ocular adnexal structures.

Breast carcinoma

Breast cancer – the most frequent cause of cancer-related death in women [23] – accounts for most cases of orbital metastases: 28.5–58.8% in various large studies [4,8,13]. This helps explain why orbital metastases are more common in women than in men. Though extremely rare, orbital metastasis from breast cancer has also been reported in men [24]. In one series [4], 89% of the patients with orbital metastases of breast cancer (33 of 37) had a diagnosis of breast cancer before presentation with the metastases. There is usually a relatively long time lapse between diagnosis of primary breast carcinoma and detection of orbital metastasis; the mean interval has been reported to range from 4.5 to 6.5 years [2,4]. In an unusual case [2], a latency period of 20 years was noted. Breast carcinoma can metastasize to the orbit after the primary tumor is believed to have been eradicated.

Orbital metastases from breast cancer tend to infiltrate the extraocular muscle and surrounding orbital fat, causing motility deficits. Scirrhous infiltration of the orbit can also occur, causing retraction of the globe inward and resultant enophthalmos. Approximately 10% of patients with breast carcinoma metastatic to the orbit present with enophthalmos [4]. The association between an enophthalmic presentation and scirrhous adenocarcinoma is well documented in the literature, but it is important to recognize that this variant may also produce proptosis rather than enophthalmos.

The histology features of adenocarcinoma of the breast vary, and the histologic features of orbital metastases may differ from those of the primary tumor. Orbital metastatic cells are usually undifferentiated anaplastic cells showing single-file infiltration of fat or dense lakes of cellular lobules [2,4]. In a report by Garrity *et al.* [4], 94% of cases (35 of 37) were anaplastic grade 3 or grade 4 tumors.

The presence of orbital metastases portends a poor prognosis: the mean survival after diagnosis of such metastases is 31 months (range, 1–116 months) [4,24]. Even if the orbit is the only clinically suspected site, it is likely that micro metastases have already occurred elsewhere. Exceptional cases of very long survival with no detectable disease in other organs, however, can occur (Fig. 5).

The only appropriate surgical intervention for breast carcinoma metastatic to the orbit is biopsy to establish the diagnosis. External-beam radiotherapy to stabilize the orbital metastatic lesion is the mainstay therapy. Chemotherapy or hormonal therapy may be administered, depending on the overall disease burden.

Lung carcinoma

Lung cancer, the incidence of which is increasing [23], is the second most common carcinoma to metastasize to the orbit, causing 8–12% of orbital metastatic lesions. Compared with breast carcinoma, lung carcinoma tends to metastasize to the orbit earlier after diagnosis and is associated with a shorter median survival time (188 versus 666 days) [4,25]. Orbital metastases from lung carcinoma have an aggressive presentation, with displacement of the globe.

Carcinoma of the lung has four principal variants: adenocarcinoma, squamous cell carcinoma, large cell undifferentiated carcinoma, and small cell lung carcinoma (SCLC). The types most likely to metastasize are large cell undifferentiated and SCLC; squamous cell and adenocarcinoma have a low incidence of metastasis [2,4]. Determination of histologic variant is important as this information influences the choice of chemotherapy regimen were chemotherapy to be used.

As life expectancy is short in patients with metastatic lung carcinoma, palliative orbital radiotherapy is the only real therapeutic option for patients with metastasis to the orbit or ocular adnexa. Exenteration is reserved for severe cases of intractable orbital pain and should be avoided if at all possible.

Prostate carcinoma

Prostate carcinoma accounts for 3–10% of orbital metastases encountered in clinical practice [4,26]. Most authors [3,4,7,9] report that prostate cancer is the third most common tumor to metastasize to the orbit; in one large series [8], prostate cancer was the second most common cancer to metastasize to the orbit. In some other series [3,8], however, prostate cancer metastasis to the orbit is reported to occur less commonly than melanoma metastatic to the orbit.

Presenting symptoms of orbital metastasis from prostate cancer include proptosis, pain, diplopia, eyelid swelling, decreased vision, ptosis, and a red eye. Pain is more common than with orbital metastases from other cancers

because prostate cancer tends to spread to orbital bone rather than orbital soft tissue. Lesions tend to present in an osteoblastic manner, though osteolytic lesions are also possible. When an osteoblastic lesion presents, it may simulate meningioma, especially if the sphenoid bone is affected. The rapid development of osteoblastic orbital lesions in an elderly man is highly suggestive of metastatic prostate carcinoma [4].

Some patients with metastatic prostate cancer will also exhibit nocturia, weight loss, and pain. The prostate-specific antigen level will often be high. Acid phosphate levels are abnormal in more than 80% of patients with distant metastases from prostate cancer.

Nearly all prostate cancers are adenocarcinomas; they may range from well to very poorly differentiated. Recognition of metastatic prostate cancer is important since it can sometimes be managed safely and effectively with hormonal therapy. Prostate cancer is a radiosensitive malignancy, and treatment for orbital disease usually consists of radiotherapy combined with hormonal therapies.

Melanoma

Orbital metastases from cutaneous malignant melanoma represent 5.3–15% of all metastatic tumors of the orbit [3,8,15]. Orbital involvement generally occurs in patients with disseminated end-stage disease and is rarely the initial sign of metastatic melanoma. The site of origin of a metastatic melanoma to the orbit is usually the skin anywhere in the body but can also be a mucosal site or the uveal tract [4,27].

In three published series, the mean intervals between treatment of the primary tumor and diagnosis of symptomatic orbital metastases were 31, 36, and 65 months [5,15].

The clinical signs of orbital metastatic melanoma are similar to those of other orbital metastatic lesions except that melanoma is more likely to involve extraocular muscle. In one series [3,15], metastasis to extraocular muscles was seen in more than half of patients with cutaneous melanoma metastatic to the orbit and ocular adnexa. This pattern of metastasis would explain why diplopia is so often the main presenting symptom in these patients. Computed tomography demonstrates smooth enlargement of the muscle rather than an infiltrative pattern into the orbit. Histologically the cells tend to be predominantly epitheliod, but it is not unusual to see an amelanotic pattern. Histochemical stains and electron microscopy may be helpful in distinguishing these differing patterns. Another frequent presentation is metastasis of cutaneous melanoma to eyelid and periocular soft tissues (Fig. 3).

The survival of patients with melanoma metastatic to the orbit depends on the extent of metastatic disease and overall disease burden but generally does not exceed 12 months. The mean survival in one series, however, was 19.7 months – much longer than the 5.75 and 8.4 months reported in two other published series [9,15].

In certain cases, surgical resection to debulk the mass, even if incomplete, may be appropriate as a palliative measure. In the case of an isolated eyelid or orbital soft tissue metastasis with no other detectable sites of metastasis, complete surgical resection of the mass followed by radiotherapy with doses of 30–60 Gy would be appropriate to achieve local control [25,26]. In patients with high disease burden and multiple metastatic sites with poor life expectancy, radical surgery is generally not indicated and may in fact worsen quality of life. Local control of an orbital metastasis with adjuvant proton-beam radiotherapy after surgical resection has also been reported.

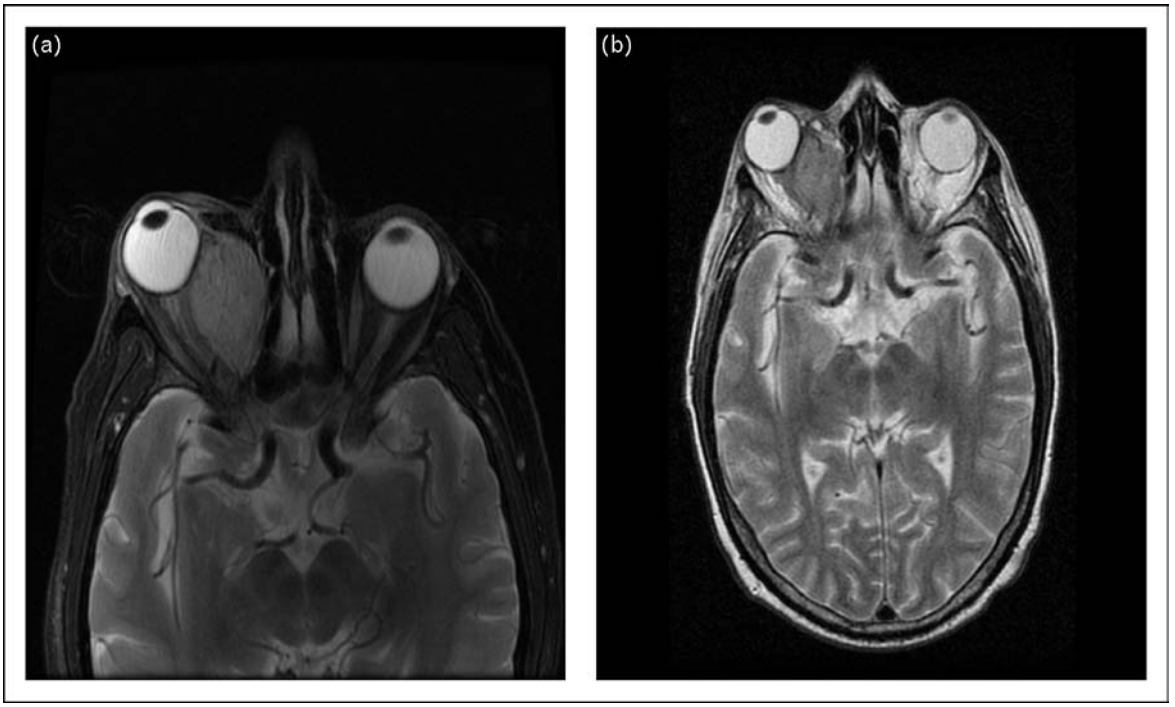
Though melanoma has traditionally been considered a chemoresistant tumor, various trials of immunotherapy or standard chemotherapy for metastatic melanoma are available at comprehensive cancer centers and should be considered for patients with melanoma metastatic to the orbit and ocular adnexa in consultation with a melanoma medical oncologist.

Carcinoid

Carcinoids are unusual tumors that arise from enterochromaffin cells and account for 4–5% of all orbital metastases [3,28,29•]. Two-thirds of carcinoids originate from the gastrointestinal tract; other sites of origin include lung, ovary, thymus, and breast [28]. Orbital metastases of carcinoid are usually from a gastrointestinal site; metastases of gastrointestinal origin accounted for 85% of cases (11 of 13) in one large series [29•]. More than two-thirds of patients with carcinoid metastatic to the orbit present with an established diagnosis. The peak incidence of such metastases occurs in the sixth decade, and there is a slight female predominance.

Metastatic orbital lesions from carcinoid are usually slow growing and may present with a mass causing proptosis (Fig. 8), diplopia, or less commonly, inflammatory symptoms. Carcinoid cells secrete bioactive amines that cause a constellation of systemic symptoms, including vasomotor disturbances, intestinal hypermotility, asthma, and paroxysmal facial flushing. Urinalysis may show an elevated urinary 5-hydroxyindole acetic acid level. A search for co-existing disorders should be conducted as carcinoids can be associated with multiple endocrine neoplasia (either type 1 or 2) and neurofibromatosis type I. Histologically, carcinoids have typical abundant granular cytoplasm with nuclear stippling [2].

Figure 8 Clinical trial of an experimental agent



(a) Magnetic resonance image demonstrates a large mass in the intraconal space, which represents metastatic carcinoid tumor of the right orbit. The patient received standard chemotherapy and radiotherapy, which produced no response. He was then treated in a clinical trial of an experimental agent, which produced a clinical and radiographic response at all his metastatic sites, including the orbit (b).

Standard treatment is local radiotherapy with combination chemotherapy. External-beam radiotherapy has been reported to be helpful in palliative local control of solitary orbital carcinoids [29•]. Standard chemotherapy has a variable degree of efficacy. Novel treatment trials may play a role in future therapy for neuroendocrine cancer. The 5-year survival rate for patients with orbital metastasis from carcinoid is 72% [29•]. Death is usually secondary to cardiac toxicity rather than from the cancer itself.

Other cancers

Virtually any cancer that can metastasize through the hematogenous route can gain access to the orbit and periocular soft tissues. A variety of cancers besides those already discussed have been reported to metastasize to the orbit. Gastrointestinal cancers are a common cause of metastasis to the orbit in Japan [2,4,13,30,31]. Renal cell carcinoma is the most common urologic malignancy to metastasize to the orbit [2,4,32,33•]. In the pediatric population, neuroblastomas and rhabdomyosarcomas have been reported to metastasize to the orbit [2,4]. As for the more common entities discussed earlier in this review, the management options for these unusual entities depend on the systemic disease load and the histologic type of the tumor. In most cases, treatment will consist of palliative radiation therapy or systemic chemotherapy.

Conclusion

Orbital metastasis is rare. In up to 25% of patients with orbital metastatic lesions, orbital metastasis is the initial presentation of previously undiagnosed cancer. Breast, lung, and prostate carcinomas and cutaneous melanoma are the leading causes of orbital metastases. Clinical manifestations of orbital metastases include rapid onset of orbital symptoms including mass effect with displacement of the globe or proptosis, diplopia, orbital pain, inflammation, and bony destruction. Infiltrative scirrhous carcinoma of the breast metastatic to the orbit may cause enophthalmos. Orbital metastasis from lung cancer tends to occur early in the disease course, whereas for breast cancer or melanoma, there is generally a long latency period between diagnosis of the primary tumor and discovery of the orbital metastasis. Imaging studies may be helpful in diagnosing orbital metastases but are nonspecific. Fine needle aspiration biopsy or open biopsies provide the best means to obtain a definitive diagnosis, but should only be done in patients with no known previous history of cancer and in patients in whom the orbit is the only site of suspected metastasis in whom having a definitive diagnosis would change the overall management of the patient. The goal of treatment for orbital metastatic lesions is palliative, and the mainstay of treatment is external-beam radiotherapy, which is combined with chemotherapy or hormonal therapy when appropriate. Surgical

resection of an orbital or eyelid metastatic lesion is appropriate only in selected patients with metastatic cutaneous melanoma or some types of metastatic sarcoma for whom the ocular adnexa is the only site of detectable metastasis.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 439).

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