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REVIEW ARTICLE

Ophthalmic Manifestations of Multiple Myeloma.

Ophtalmiques Manifestations de myélome multiple

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ABSTRACT

BACKGROUND: **The ophthalmic manifestations of multiple myeloma can be seen in practically every ocular structure. Ocular findings may be the first manifestations of the disease. It may also occur as one of the extramedullary manifestations of the disease or as the first sign of insufficient chemotherapy. Multiple myeloma may cause ocular pathology by direct infiltration or as extramedullary plasmacytomas resulting in displacement or compression of tissues, by causing hyperviscosity syndrome, and by immunoglobulin light chain deposition in ocular tissues.**

OBJECTIVE: **To outline the ophthalmic manifestations of multiple myeloma.**

METHODS: **Information about multiple myeloma and ophthalmic manifestations was obtained from original journal articles, review articles, case reports and standard postgraduate textbooks.**

RESULTS: **Ophthalmic manifestations include proptosis, diplopia, lid ecchymosis, xanthomatosis, conjunctival and corneal crystalline and non-crystalline deposits, scleritis, episcleritis, secondary glaucoma, ciliary body cysts, ciliochoroidal effusion, uveal plasmacytoma, hyperviscosity retinopathy, retinal vasculitis, detachment of sensory retina and retinal pigment epithelium, and neuro-ophthalmic manifestations.**

CONCLUSIONS: **In multiple myeloma, it is necessary to take a closer look at the ophthalmic manifestations, both because of their local morbidity and because they might act as a reservoir for proliferation of myeloma cells and eventual systemic relapse. Early detection may permit safer and effective treatment. All patients with multiple myeloma should thus undergo thorough ophthalmic examination at the time of initial diagnosis and during follow-up. WAJM 2007; 26(4): 265–268.**

Keywords: ***Ophthalmic manifestations, multiple myeloma, hyperviscosity syndrome.***

RESUME

HISTORIQUE: Le ophtalmiques manifestations du myélome multiple peut être vu dans la quasi totalité des structures oculaires. Ocular conclusions peuvent être les premières manifestations de la maladie. Il peut également se produire comme l'un des extramédullaire manifestations de la maladie, ou comme le premier signe de l'insuffisance de la chimiothérapie. Le myélome multiple peut causer pathologie oculaire direct par infiltration ou extramédullaire plasmacytomas comme à l'origine du déplacement ou la compression des tissus, en provoquant le syndrome d'hyperviscosité, ainsi que par l'immunoglobuline chaîne légère des dépôts dans les tissus oculaires

***OBJECTIF:** décrire les manifestations ophtalmiques de myélome multiple.*

***MÉTHODES:** Des informations sur le myélome multiple et ophtalmiques manifestations originales ont été obtenues à partir des articles de revues, les articles de synthèse, les rapports de cas et le niveau postuniversitaire manuels.*

***RÉSULTATS:** Ophthalmic manifestations comprennent proptose, diplopie, couvercle ecchymose, xanthomatosis, de la conjonctive et la cornée, cristallin et de la non-dépôts cristallins, sclérite, épisclérite, glaucome secondaire, corps ciliaire kystes, ciliochoroidal épanchement, uveal plasmocytome, hyperviscosité rétinopathie, vascularite rétinienne, le détachement de sensorielle Rétine et l'épithélium pigmentaire rétinien, et neuro-ophtalmologiques manifestations.*

CONCLUSION:** Dans le myélome multiple, il est nécessaire de regarder de plus près les manifestations ophtalmiques, à la fois en raison de leur morbidité et locales car ils peuvent agir comme réservoir de la prolifération des cellules myélomateuses et systémique éventuelle rechute. Le dépistage précoce peut permettre un traitement sûr et efficace. Tous les patients atteints de myélome multiple doivent donc subir un examen ophtalmologique complet au moment du diagnostic initial et au cours du suivi. **WAJM 2007; 26(4): 265–268.

***Mots-clés:** manifestations ophtalmiques, le myélome multiple, le syndrome d'hyperviscosité.*

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Abbreviations: MM, Multiple Myeloma

INTRODUCTION

Multiple myeloma (MM) is one of the most common haematologic disorders characterized by proliferation of a clone of plasma cells that manifests by the presence of one or more lytic bone lesions, monoclonal (M) protein in the blood/urine and bone marrow involvement.[1] The occurrence of MM is worldwide and is more commonly seen in Blacks than in the Caucasians.[2] It is the second most prevalent blood cancer after non-Hodgkin's lymphoma, causing 2% of all cancer deaths.[3] MM accounts for approximately 1% of all human cancers and 10% of all haematological malignancies, ranking 13th and 17th among cancer sites in men and women respectively.[4] The current therapeutic approach, especially with the advancement in high-dose chemotherapy and stem cell transplant have improved overall survival and event-free periods, but relapse is inevitable.[5]

The diagnosis of multiple myeloma is generally straightforward. Recurrent infections, anaemia, renal insufficiency or osteolytic bone lesions commonly lead to the discovery of abnormal plasma cells in the bone marrow.[6,7] Rarely, the serum monoclonal protein level remains lower than 3.0g/dl with no signs or symptoms of the disorder, and bone marrow biopsy reveals less than 10% plasma cells. This condition is referred to as monoclonal gammopathy of undetermined significance, and progression to MM or a related disorder occurs at a rate of approximately 1% per year.[8]

Occasionally, ocular findings may be the first manifestations of the disease.[9,10] It may also occur as one of the extramedullary manifestations of the disease,[11,12,13] or as a first sign of insufficient chemotherapy.[14] The proteinaceous material has been identified in practically all parts of the eye as immunoprotein using an immunoperoxidase technique.[15] Thus the ophthalmic signs of MM can be seen in every ocular structure.[16]

Since longer survival is now achievable with modern therapeutic measures, it has become necessary to take a closer look at sites of extramedullary involvement including the eyes, both because of their local morbidity and because they might act as a reservoir for proliferation of myeloma cells and eventual systemic relapse. Early detection may permit safer and equally effective treatment. All patients with MM should thus undergo thorough ophthalmic examination at the time of initial diagnosis.[17] It has therefore become appropriate to review the ocular manifestations of MM. This will assist the ophthalmologist to play a pivotal role in the prompt diagnosis and treatment of MM especially in those presenting with ocular features. It will also assist the haematologist to recognize the need for a complete ophthalmic evaluation in the diagnosis and management of these patients.

Multiple myeloma (MM) accounts for 2.9% of all malignancies in Blacks and 1.0% in Whites.[18] The USA average annual age-adjusted incidence rates per 100,000 are 10.2 for Black males and 6.7 for Black females, 4.7 for White males and 3.2 for White females.[18] Orbital involvement in MM is rare and affects older individuals usually.[19] In one series that cites a median age of 56 years, the youngest patient was 30 years old.[19] In another recent study, the mean age was 61.25 years (range 42-78years).[11] As much as 75% of the patients with ophthalmic manifestations were known to have MM at the time of ophthalmic evaluation. However, orbital manifestations has been reported in a 19 year old pregnant black female who presented initially with proptosis and diplopia.[19] Cysts of the ciliary body have been reported in 33-50% of myeloma patients, and retinal vascular lesions have been reported in up to 60%.[13]

MECHANISM OF OCULAR MANIFESTATIONS

Cancer may affect the eye and orbit by a direct effect of metastatic neoplastic infiltration or by compression or by circulating antibodies involving paraneoplastic retinal degeneration.[20] One of the mechanisms by which MM affects the orbit and ocular tissues is by direct infiltration or as extramedullary plasmacytomas.[10,21-23] The resultant mass lesion can cause displacement or compression of tissues.[14] Another mechanism is by causing hyperviscosity syndrome.[24] Hypergammaglobulinaemia increases serum viscosity and is the most common cause of hyperviscosity syndrome. The reasons for elevated viscosity are increased protein content and large molecular size, abnormal polymerization, and abnormal shape of immunoglobulin molecules. Other haematologic and metabolic abnormalities seen in patients with plasma cell dyscrasias also contribute to hyperviscosity. Symptomatic hyperviscosity occurs in 2-6% of MM patients.[24] The main sequel of circulating disturbances caused by increased blood resistance to flow include fundus alterations (55.6%), neurologic manifestations (88.9%), a tendency to bleeding (44.4%) and renal failure (55.6%).[25]

Furthermore, immunoglobulin light chains can be deposited in ocular tissues.[26] Using light microscopy, electron microscopy, and immunohistochemical studies, monoclonal kappa immunoglobulin light chains have been demonstrated in the cornea,[26] conjunctiva,[27] beneath the basement membrane of the ciliary pigment epithelium, on vessels of the ciliary body, within the collagenous zones of Bruch's membrane, and in the innermost part of the choroid.[28] They have also been identified in the anterior chamber, ciliary body cysts, choroid and ciliary body, subretinal and subretinal pigment epithelial areas.[15]

OPHTHALMIC MANIFESTATIONS

MM can present as pathology in practically all the orbital and ocular tissues. Early identification and early treatment is necessary to prevent irreversible visual loss. The ophthalmic manifestations will be reviewed under the subheadings of orbit and adnexia, anterior segment, posterior segment and neuro-ophthalmic manifestations.

Orbital involvement by MM is rare and usually affects older individuals.[19,29] They may cause mass lesion large enough to cause displacement of the globe leading to proptosis and diplopia.[14,22] In a patient with proptosis and known MM, an orbital mass can be presumed to be orbital involvement by multiple myeloma.[12] Proptosis may either be the initial manifestation that led to the diagnosis of

the disease or may occur as a terminal event or may even be the first sign of insufficient chemotherapy.[10,14] MM involving the skull base can also extend into the orbit and cause proptosis.[30] CT scan of this lesion shows a large extracranial soft-tissue mass, intracranial extension, homogenous enhancement, smooth margins and bone remodeling.[30]

Bilateral eyelid ecchymosis has been reported in a 55-year-old man after he flexed 90 degrees at the waist and this eventually led to diagnosis of MM.[9] Cutaneous xanthomatosis may occur in association with MM.[31] Necrobiotic xanthogranuloma with paraproteinaemia is characterized by multiple nodules or plaques that involve the periorbital area along with other parts of the body, and may be associated with MM.[32,33] In one series, 15 of 16 patients with this condition had ophthalmic manifestations.[33] Thirteen patients had lesions affecting the skin of the eyelids and periorbital tissues; on examination these lesions resemble plane xanthoma. Unlike plane xanthoma, however, the lesions of necrobiotic xanthogranuloma are almost always indurated. Furthermore, the lesions frequently become inflamed, leading to superficial ulceration. Deeper lesions occasionally involve the orbit.[33] Surgical excision of eyelid lesion is often associated with recurrence and increased activity of the lesions. Because necrobiotic xanthogranuloma with monoclonal gammopathy frequently has prominent manifestations in the orbital region, it may result in dysfunction of the eyelids or extraocular muscles and is associated with potentially life-threatening systemic conditions, its recognition by the ophthalmologist is important.[32] Low-dose chemotherapy is likely to produce favorable response, with regard to both skin lesions and the paraprotein abnormalities.[33]

Conjunctival involvement in MM is rare.[10] Minimal conjunctival changes may be the first indication of neoplastic proliferation of plasma cells in the eye.[10] There may be conjunctival crystalline deposits which on light microscopy are revealed to be plasmacytoid infiltrates and stain monoclonally for immunoglobulin G-kappa light chains.[27] Solitary plasmacytoma may also occur in the conjunctiva.[21]

Corneal deposits may be the initial manifestation of MM.[9,26,27,34] The appearance of the deposits is variable. It may be crystalline [9,27,34] or non-crystalline.[26] The distribution of the corneal crystals is also variable. They may be dispersed centrally and peripherally throughout all levels of the cornea,[9] or may be limited to the superficial corneal epithelium.[34] It may also be one of the causes of vortex keratopathy (cornea verticillata).[27] The keratopathy of MM may masquerade as corneal crystals of ocular cystinosis,[34] but the corneal crystals of MM usually do not cause ocular irritation in contrast to the intense discomfort caused by corneal crystals of cystinosis.[34,35] The corneal crystals have been identified as consisting of immunoglobulins, primarily IgG, but the pathophysiology of crystal formation remains enigmatic.[34,36,37] Some data suggest that elevated immunoglobulin levels in tears or aqueous humour lead to corneal crystals , while other data suggest that the immunoglobulins reach the cornea through limbal vessels or that keratocytes supply the precipitated immuno-globulins.[34] Alternatively, MM may present as subepithelial amorphous corneal deposits as well as diffuse noniridescent anterior stromal haze of unknown aetiolgy.[26] The deposits were also identified as monoclonal IgG kappa immunoglobulins.

In necrobiotic xanthogranuloma, yellowish lesions are sometimes visible in the episcleral tissues where they are associated with recurrent symptoms of scleritis and episcleritis.[33]

Intraocular pressure may be elevated secondary to an orbital mass causing indentation of the globe.[14] Proteinaceous material may accumulate in the anterior chamber.[15] This could cause secondary glaucoma due to blockage of the trabecular pores.

The iris may be the site of a plasmacytoma.[21] Cysts of the ciliary body has been reported in up to 33-50% of myeloma patients.[13] The ciliary body cysts contain immunoprotein and may be opaque.[15] A ciliochoroidal effusion has also been reported in MM with proteinaceous material in the choroid and ciliary body.[15] Massive deposits of kappa light chains have been found beneath the basement membrane of the ciliary pigment epithelium and on vessels of the ciliary body.[28] The first case of an intraocular extramedullary plasmacytoma in a cat has recently been reported. It occurred in an 8-year-old castrated male domestic shorthaired cat that presented with uveitis and an iridal mass in a blind eye.[38]

The choroid may be involved in MM.[15] The choriocapillaries in the macular area may be partly obstructed by massive deposits of kappa light chains and an exudative retinal detachment may be present.[28] Whether this detachment is the consequence of disturbed circulation of the choriocapillaries remains speculative.

Retinal vascular disorders have been reported in up to 66% of patients with MM.[13] In one series, hyperviscosity retinopathy was reported to constitute 12.5% of ophthalmic manifestations of MM.[11] Retinal features of hyperviscosity include venous dilatation, segmentation and tortuosity, superficial and deep haemorrhages, cotton-wool spots, retinal vein occlusion and disc oedema. Retinal microaneurysms and detachment of both the sensory retina and the retinal pigment epithelium may occur.[15] Immunoprotein has been identified in the subretinal and subretinal pigment epithelial areas.[15] Retinal vasculitis has also been reported to be associated with MM.[31]

Neurological manifestations are not unusual in MM.[39] Meningeal involvement occurs in patients with initially stage III MM in 85% of cases. The most frequent neurologic signs are confusion (60%), altered consciousness (25%), gait disorder (25%) and cranial nerve palsy (25%).[39] Any of the cranial nerves supplying the eye may be affected resulting in diplopia and visual disturbances.[11] These neuro-ophthalmic symptoms has been reported to occur in up to 50% of patients with ocular manifestations of MM. Temporal arteritis may also occur in association with MM and give rise to neuro-ophthalmic symptoms.[31]

CONCLUSION

Most of the ophthalmic tissues can be affected by MM. The ophthalmic manifestation may be the first symptom

of the disease, an extramedullary manifestation of the systemic disease or the first symptom of insufficient chemotherapy. The ophthalmic manifestations are due to mass lesions (plasmacytoma), infiltration by myeloma cells, massive deposition of monoclonal kappa light chain immunoglobulins in ocular tissues, hyperviscosity syndrome and associated lesions such as necrobiotic xanthogranuloma and vasculitis. Awareness of the possible manifestations may lead to an earlier diagnosis and have a positive influence on the course of the disease. Thus, all patients with MM should undergo thorough ophthalmic examination at the time of initial diagnosis.

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