Unusual presentation of more common disease/injury

Ophthalmic manifestations of atypical IgD multiple myeloma

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Summary

A previously healthy 32-year-old Caucasian female presented with sudden-onset horizontal diplopia following a paroxysm of coughing. She had recently sustained a pubic ramus fracture during an innocuous fall and had also noted a firm lump developing at the right side of her forehead. On examination, she had a right fronto-temporal mass. Visual acuities were 6/6 bilaterally. There was reduced abduction of the right eye, bilateral white, granular corneal opacities and evidence of bilateral optic disc swelling. Haematological investigations revealed normocytic anaemia, hypercalcaemia and raised erythrocyte sedimentation rate (ESR). CT showed lytic foci throughout the skull, ribs, scapulae, spine, pelvis and upper femora. Serum protein electrophoresis revealed immunoglobulin D (IgD)-kappa paraproteinaemia; urine electrophoresis showed free light chain kappa and bone marrow biopsy demonstrated 87% plasma cells. A diagnosis of IgD multiple myeloma was made, with subsequent chemotherapeutic treatment and eventual autologous stem cell transplant resulting in resolution of neuro-ophthalmic manifestations and prolonged disease remission.

BACKGROUND

Multiple myeloma is a neoplastic proliferation of malignant plasma cells that secrete monoclonal paraprotein.¹ Multiple myeloma usually presents with systemic symptoms including fatigue, anorexia, weight loss and bone pain, but previous reports have also established that every ocular structure may exhibit signs of multiple myeloma.

Ophthalmic abnormalities in the context of multiple myeloma are variable and diverse but rare. We report the unusual case of a young female who presented with a range of ophthalmic manifestations—right lateral rectus palsy, bilateral subepithelial corneal infiltrates and bilateral optic disc swelling—and was subsequently diagnosed with the rare, immunoglobulin D form of multiple myeloma, an entity with a poor prognosis that usually afflicts middle-aged males.^{2–5} We discuss the underlying pathogenesis of the ophthalmic features and provide a comprehensive literature review of previously reported ophthalmic, neuro-ophthalmic and orbital manifestations of multiple myeloma.

CASE PRESENTATION

A previously healthy 32-year-old Caucasian female presented with sudden-onset horizontal diplopia following a paroxysm of coughing. There was no headache, visual loss, ocular pain or peripheral neurological symptoms. She had no systemic upset or weight loss. She had recently sustained a right pubic ramus fracture as a result of an innocuous fall and had also noted a firm lump developing at her right fronto-temporal region.

On examination, she had a 5×3 cm firm, rubbery, non-tender, non-pulsatile, non-transilluminable mass at the right fronto-temporal region (figure 1). Visual acuities were 6/6 bilaterally. There was reduced abduction of the right eye, in keeping with lateral rectus palsy. There was no proptosis. Pupils were equal and reactive to light and accommodation with no relative afferent pupillary

defect. Colour vision and remaining cranial nerve examination were normal. Both eyes were quiet with normal intraocular pressures. There were white granular corneal opacities noted at the Descemet's membrane level bilaterally (figure 2). Dilated fundal examination revealed bilateral optic disc swelling with an absence of spontaneous venous pulsation.

INVESTIGATIONS

Routine haematological tests indicated normocytic anaemia (Hb 9.6 g/dl, mean cell volume (MCV) 83 fl), hypercalcaemia (3.16 mmol/l), and elevated ESR (119 mm/h). CT of the head showed numerous lytic foci scattered throughout the skull base, involving the pituitary fossa and extending into the right sphenoid sinus. The largest lesion was found to be arising from the right frontal bone, eroding both inner and outer bone tables and compressing the right frontal lobe

Figure 1 Photograph demonstrating the diffuse mass at the right fronto-temporal region. The mass was of gradual onset and was painless and non-pulsatile on examination. There was no previous history of head trauma.

Figure 2 Slit lamp examination of the right eye at initial presentation. Multiple punctate white deposits were found scattered at the Descemet's membrane level. Equivalent findings were observed in the left eye (not shown).

(figures 3 and 4). Subsequent serum protein electrophoresis revealed an immunoglobulin D (IgD)-kappa paraproteinaemia (16.7 g/dl) and urine electrophoresis showed a free light chain kappa. CT of chest, abdomen and pelvis demonstrated diffuse lytic deposits throughout the ribs, scapulae, spine, pelvis and upper femora. However, there was no lymphadenopathy or abnormality of the lungs, liver or spleen. Bone marrow examination revealed 87% plasma cells.

OUTCOME AND FOLLOW-UP

The patient was subsequently diagnosed with stage IIIB IgD multiple myeloma (by the Durie-Salmon staging system) and started on treatment with cyclophosphamide, dexamethasone and thalidomide. The mass at the

Figure 3 Coronal CT head image at initial presentation. A lesion arising from the right frontal bone, eroding both inner and outer bone tables and compressing the right frontal lobe is clearly visible.

Figure 4 Reconstructed CT image demonstrating a large right fronto-temporal bony defect and multiple lytic lesions of the skull.

right fronto-temporal region decreased in size, diplopia resolved and the abduction deficit improved, vision remained normal throughout. Although the optic disc swelling resolved, the corneal opacities remained unchanged. She subsequently underwent autologous stem cell transplantation. Despite relapsing twice in the first two years following treatment, the patient is currently in remission, six years later.

DISCUSSION

Multiple myeloma is a neoplastic proliferation of malignant plasma cells that secrete monoclonal paraprotein. It accounts for about 10% of haematological malignancies, with an incidence of 5.5 cases per 100 000. The median age at diagnosis is 70 years and only 3.4% of cases are diagnosed between 35 and 44 years of age.¹ Common presenting symptoms of multiple myeloma include generalised fatigue, anorexia, weight loss and bone pain (particularly of the lumbar spine). Blood tests may show normocytic anaemia, deranged renal function and hypercalcaemia. There may be Bence-Jones proteinuria and a monoclonal immunoglobulin spike on serum protein electrophoresis.¹

IgD multiple myeloma is relatively uncommon, comprising only 1–2% of all reported cases and is generally considered to have a poorer prognosis than other forms of multiple myeloma.^{2–5} IgD multiple myeloma predominantly affects men, usually in the 55–60 years age group, with approximately 67% of patients presenting prior to the age of 60 years.² IgD multiple myeloma is associated with a more aggressive disease, worse response to chemotherapy and poorer prognosis, with a median survival from diagnosis of 13–21 months.⁴ It is more likely to be associated with lymphadenopathy, hepatomegaly, renal failure, hypercalcaemia, amyloidosis and extraosseous plasmacytomas than other isotypes.^{3–4}

Every ocular structure may exhibit signs of multiple myeloma.⁵ Numerous ophthalmic features have been

described in the literature (table 1) and have previously been classified into opportunistic (ocular infections secondary to immunosuppression), ocular, orbital and neuro-ophthalmic.⁵ Our patient presented with three of these—a right lateral rectus palsy, bilateral subepithelial corneal infiltrates and bilateral optic disc swelling.

Bilateral optic neuropathy has previously been described in the context of multiple myeloma,⁵ as have third and sixth cranial nerve palsies.^{6–7} It has been proposed that such neuro-ophthalmic features may occur in multiple myeloma either through a haematological process due to hyperviscosity from increased circulating plasma proteins, a microvascular effect, a direct compressive effect at the skull base, cavernous sinus or orbital apex by intracranial plasmacytoma, elevated intracranial pressure or otherwise meningeal infiltration.⁸ In the case of our patient, both

the lateral rectus palsy and the optic disc swelling resolved during and following treatment, as did the large lesion of the right frontal bone, meaning that it is impossible to precisely discern the pathophysiology of her neuro-ophthalmic signs. Irrespective of this, Fung *et al*⁸ reported eight cases of multiple myeloma with ophthalmic manifestations, three of whom had cranial nerve palsies (oculomotor or abducens nerve). Furthermore, five of these patients died within two months of their ophthalmic presentation.

Our patient also had bilateral subepithelial corneal infiltrates, apparently at the Descemet's membrane level. Generalised corneal haze,⁹ prominent corneal nerves and reduced corneal sensitivity,¹⁰ vortex keratopathy,¹¹ intracorneal copper deposits^{12–15} and crystals dispersed centrally and peripherally throughout all levels of the cornea^{14–15} have all previously been reported. Such corneal crystals have been shown to be deposits of monoclonal IgG kappa^{9–11–13–15} or lambda¹⁴ immunoglobulin, and may cause such visual morbidity to require penetrating keratoplasty.¹⁶ Confocal microscopy studies have shown these infiltrates to be hyper-reflective globules¹⁷ or needle-like structures¹⁸ which are typically located in the corneal epithelium and anterior stroma, obscuring the normal corneal architecture but being reduced in size and number following chemotherapeutic treatment.^{17–18} Unfortunately, it has been reported that these crystals may recur in a corneal graft.^{14–16}

With advances in chemotherapeutic regimens, and subsequent possibility of increased patient survival, it is increasingly important to have an awareness of the ophthalmic features of multiple myeloma in order to make an earlier diagnosis, not only to have a potentially positive influence on the course of the disease but also to more effectively treat visual morbidity that may significantly affect the quality of life.

Table 1 Summary of previous ophthalmic, neuro-ophthalmic and orbital manifestations of multiple myeloma reported in English language medical literature

Ophthalmic feature	Reference
Orbit/adnexa	
Lacrimal sac infiltration	19
Bilateral proptosis	20
Plasmacytoma of the orbit	21–23
Orbital amyloidosis	24
Lids/periocular structures	
Bilateral eyelid ecchymoses	25
Necrotising eyelid lesion	26
Eyelid necrobiotic xanthogranuloma	27
Conjunctiva	
Salmon patch conjunctival mass	28
Episcleral necrobiotic xanthogranuloma	27
Cornea	
Prominent corneal nerves	10
Copper deposition	12–13
Crystalline keratopathy	14–16–25–29
Vortex keratopathy	11–30
Anterior chamber	
Recurrent uveitis	14
Hypertensive uveitis	31
Pseudohypopyon	32–33
Uveal tract	
Ciliary body cysts	34
Plasmacytoma of the uvea	35–36
Copper deposition on iris	13
Lens capsule	
Copper deposition	13–12
Posterior segment	
Bilateral exudative macular detachment	37
Central retinal vein occlusions	38–39
Neuro-ophthalmic	
Cavernous sinus syndrome	40
Oculomotor nerve palsy	7
Abducens nerve palsy	6–41
Bilateral optic neuropathy	5

Learning points

- Ophthalmic abnormalities in the context of multiple myeloma are variable and diverse, but rare. Every ocular structure may exhibit signs of multiple myeloma.
- The immunoglobulin D form of multiple myeloma is uncommon and generally considered to be more aggressive and have a poorer prognosis than other myeloma isotypes. It predominantly affects men, usually in the 55–60 years age group and is more likely to be associated with lymphadenopathy, hepatomegaly, renal failure, hypercalcaemia, amyloidosis and extraosseous plasmacytomas.
- Neuro-ophthalmic features may occur in multiple myeloma either because of blood hyperviscosity, a compressive effect by intracranial plasmacytoma at the skull base, cavernous sinus or orbital apex, secondary to elevated intracranial pressure or otherwise by direct meningeal infiltration.
- Corneal infiltration by monoclonal immunoglobulin G crystals in multiple myeloma, principally to the epithelium and anterior stromal layers, may cause such visual morbidity as to require penetrating keratoplasty. Unfortunately, it has been reported that these crystals may recur in a corneal graft.

Competing interests None.

Patient consent Obtained.

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