Case report

Corneal opacity and copper levels of the Lewis syndrome after systemic chemotherapy

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ABSTRACT

Purpose: To report a female patient of biclonal Lewis syndrome which consists of a triad: biclonal gammopathy of undetermined significance, paraproteinemnic keratopathy in form of a brownish discoid discoloration in the Pre-Descemet’s layer. The corneal findings were unchanged after a follow up of eight years. However, there was a conversion to multiple myeloma (MM) type IgG with progressive anemia and suspicious bone lesions. A multiple systemic myeloma-therapy was indicated. Chemo therapy with subsequent tandem autologous-stem cell therapy (auto-SCT) was performed. The blood examination after this therapy showed a complete remission of multiple myeloma, and it was also very surprising that the serum copper level was within normal range. This finding remained unchanged over a period of five years. The bilateral corneal opacification was identical to that before chemotherapy. To the best of our knowledge, this represents the first observation of a normalization of copper levels in Lewis syndrome after chemotherapy.

Conclusions and importance: The Lewis syndrome represents a very rare disorder. The first case reported in Europe (Lisch et al., 2016) showed a conversion from biclonal gammopathy of undetermined significance to MM after a follow-up of 17 years. Subjectively, the patient was in excellent health. The typical corneal, discoid brownish opacification at the level of Descemet’s membrane is a suspicious hint of a copper disturbance for the ophthalmologist. The copper level of our patient was extremely elevated. The corneal opacification however, remained unchanged throughout the repeated ophthalmological examinations. In 2015, the conversion of our case with Lewis syndrome to MM performing chemotherapy in different steps and a twice auto-SCT resulted in a complete remission of MM and a normal range of the serum copper. The bilateral corneal opacification remained unchanged during an observation period of five years after chemotherapy.

1. Introduction

Monoclonal gammapathies (MG) are malignancies of plasma cells. Normal plasma cells help to defend the body against infection. Multiple Myeloma (MM) represents one part of the spectrum of monoclonal gammapathies that includes the much larger category of monoclonal gammapathy of undetermined significance (MGUS). MGUS is one of the most frequent premalignant disorders in Western countries and occurs in approximately 3% of persons 50 years of age or older. MGUS is a hidden disorder because the patient has no subjective symptoms, and the hematologists see no reason to initiate therapy. It is proposed that regular check ups be performed annually. It is known that there is an association between MGUS and distinct corneal opacities in general, paraproteinemic keratopathy (PPK). The MM- or MGUS-induced corneal crystals have been known for many years and are to be differentiated from cystinosis and Schnyder corneal dystrophy. Other bilateral opacifications have often been confused with different corneal dystrophies. Therefore, the term MG of ocular significance was also suggested. Most of the MGUS-patients with an association of corneal opacity show serologically an IgG. One explanation could be that the IgG has a lower molecular weight than the other immunoglobulins and therefore can better penetrate into the cornea. The Lewis syndrome

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The female patient with biclonal Lewis syndrome is now 66 years old. In 2015 conversion to MM type IgG, type lambda with progressive anemia and suspicious bone lesions was diagnosed. MM-directed therapy was indicated. There were bilateral, disceous yellow-brownish corneal opacities at the level of Descemet’s membrane (Fig. 1a and b). In vivo confocal laser scanning microscopy (IVCM) of posterior stroma revealed blurred structure of the keratocytes and hyperreflective punctiform and needle-like structures that seem to be typical for para-proteinemic keratopathy (Fig. 2). The conjunctiva, retina, and intraocular pressure were normal. There were no signs of intraocular inflammation. In the meantime, an age-related cataract proceeded and best corrected visual acuity (BCVA) decreased. Uneventful bilateral cataract surgery was performed. The BCVA after cataract surgery was 20/20 bilaterally despite the corneal opacities. The histopathological examination of the anterior lens capsule of both eyes and phacoemulsified lens material of the left eye did not show any copper deposits. High performance liquid chromatography of aqueous humor did not reveal any copper. The following current serological findings were collected: IgG, type lambda 66.2 g/l (norm 7–16 g/l); IgA, type lambda and IgM below reference; M-protein 45.5 lambda g/l; free light chain lambda 51.1 mg/l (norm 5.7–26.3 mg/l); free light chain kappa 8.6 mg/l (norm 3.3–19.4 mg/l); free kappa/lambda ratio 0.2 (norm 0.3–1.6); lambda light chain in 24-h urine 34.6 mg/l; hemoglobin 9.5 g/dl (norm 3.3–16 g/dl). Serum copper levels were normal within 12 μg/dl (norm 10–60 μg/dl). Serum coeruloplasmin within 0.23 g/l (norm 0.2–0.6 g/l), urine copper levels within 12 μg/dl (norm 10–60 μg/dl) and transaminases were within normal limits. After peripheral blood stem cell mobilization with cyclophosphamide, Adriamycin, dexamethasone (CAD) and stem cell collection, tandem high dose melphalan therapy with auto-SCT was performed, followed by consolidation therapy with bortezomib, lenalidomide, and dexamethasone. A complete remission of MM was achieved. Maintenance therapy with lenalidomide was stopped because of adverse effects. The last bone marrow biopsy in 2017 revealed 3% of plasma cell infiltration. A follow-up blood examination in 2020 showed a complete remission of MM. Serum copper level was within normal range of 144 μg/dl (norm 68–169 μg/dl). A change in density of the brownish corneal opacities could not be determined after chemotherapy.
normal copper levels in the serum after the current and modern chemotherapy of MM during a follow-up of five years. To date, however, no improvement in the existing corneal changes has been observed despite normal copper levels in the blood. Subjectively, our patient was in excellent health before and after the MM treatment. Normally, copper does not bind to immunoglobulins. In the case of Lewis syndrome the IgG has a marked affinity for copper. The chemotherapy of our proband led to a complete remission of the MM and at the same time to normal copper values in the serum over five years. This is further evidence of the unique IgG nature in the context of Lewis syndrome. The Lewis IgG must have a special, unknown property with regard to copper binding. Further studies are needed to clarify this mechanism.

Patient consent
This report does not contain any personal identifying information.

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Declaration of competing interest

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