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EFFECT OF RELAPSING POLYCHONDRITIS AND LEUKEMIC INFILTRATION IN A PATIENT WITH MYELODYSPLASTIC SYNDROME

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Summary

A 56-year-old female patient with myelodysplastic syndrome is presented, in whom pathogenetically diverse mechanisms led to the development of severe sensorineural hearing loss and bilateral blindness. The patient had suffered from myelodysplastic syndrome from 2003. One year after verification of the diagnosis, she presented to the Department of Ophthalmology for ptosis and edema of the right eyelid, exophthalmia, visual impairment, and restricted ocular movement. The discomforts persisted for four weeks to result in the loss of vision. This was followed by impaired hearing in the right ear, accompanied by vertigo. Two months later, the same occurred in the left ear, preceded by visual impairment in the left eye with identical symptomatology as in the right eye. The disease eventually resulted in bilateral hearing loss and blindness. Laboratory findings were consistent with the clinical picture. Audiologic testing confirmed sensorineural deafness in the right ear first, followed by severe conductive hearing loss in the left ear. Computed tomography and nuclear magnetic resonance findings of the ear were normal. Computed tomography of the orbits showed bilateral optic nerve thickening. There was bilateral absence of visual evoked potentials and presence of relative afferent pupillary defect. Analysis of the patient's findings and comparison with literature reports suggested the role of two mechanisms, i.e. relapsing polychondritis and leukemic cell infiltration, in the pathogenesis of myelodysplastic syndrome symptomatology.

KEY WORDS: *hearing loss, myelodysplastic syndrome, optic nerve atrophy, leukemic infiltration, relapsing polychondritis*

RELAPSIRAJUĆI POLIHONDRITIS I LEUKEMIČNA INFILTRACIJA U BOLESNIKA S MIJELODISPLASTIČNIM SINDROMOM

Sažetak

Prikaz slučaja 56-godišnje bolesnice sa sindromom mijelodisplazije, u koje patogenentski dvojni mehanizmi dovode do razvoja teške senzorineuralne gluhoće i sljepoće. Sindrom mijelodisplazije se verificira 2003. godine. Godinu dana kasnije razvijaju se oteklina vjeđa, egzoftalmija, poremećaj vida i reducirani pomaci očne jabučice desnog oka. Poteškoće završavaju sljepoćom desnog oka. Sljepoća je praćena naglim gubitkom sluha na desnom uhu, s hipotonijom perifernog vestibularnog osjetila. Dva mjeseca kasnije sljepoća i gluhoća zahvaćaju lijevo oko i lijevo uho. Osnovna bolest se komplicira obostranom sljepoćom i gluhoćom. Biokemijski nalazi prate kliničku sliku. Audiološka testiranja potvrđuju senzorinerulanu nagluhost, pa gluhoću na desnom uhu, kasnije i na lijevom. Kompjutorizirana tomografija i nalaz magnetske rezonancije pokazuju uredan nalaz piramida sljepoočnih kostiju i zadebljanje očnog živca obostrano. Usporedo postoji obostrano odsutan VEP odgovor i relativni aferentni pupilarni defekt. Analiza učinjenih pretraga i usporedba sa spoznajama iz literature upućuje na sudjelovanje dvaju mehanizama, tj. relapsirajućeg polihondritisa i leukemične celularne infiltracije, u sklopu patogeneze sindroma mijelodisplazije.

KLJUČNE RIJEČI: *gluhoća, sindrom mijelodisplazije, atrofija vidnog živca, leukemična infiltracija, relapsirajući polihondritis*

INTRODUCTION

Myelodysplastic syndrome (MDS) is a group of clonal diseases that are generated through malignant transformation of one pluripotent or one multipotent hematopoietic stem cell, resulting in hematopoesis failure. Such transformation entails proliferation of a pathologic cell clone, which has a reduced ability of differentiation and maturation into mature blood cells (1). The process is characterized by progressive cytopenia or cytopenias, usually in the presence of hypercellular bone marrow and multilinear dysplasia. According to the morphological French-American-British (FAB) classification, MDS is divided into five subtypes: refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with blast excess, chronic myelomonocytic leukemia, and refractory anemia with blast excess in transformation. Chromosomal aberrations are common in MDS; however, the causal relationship with the disease has not yet been identified.

MDS is a rare hematologic disease, and its ENT and eye complications have not been fully documented. To our knowledge, only one case of hearing loss in myelodysplasia along with sclerosing scleritis and amaurosis as likely sequels of a relapsing polychondritis (RPC) has been described to date (2). Cases of orbital inflammation with proptosis and of exophthalmos with conjunctival chemosis, restricted eye movement, and decreased visual acuity have been reported (3, 4). Two patients with the picture of acute glaucoma as an initial manifestation of MDS (5, 6), one patient with birdshot retinopathy (7), and one patient with choroid infiltration (8) have been described. All cases with ocular pathology are explained by the pathogenetic mechanism of leukemic infiltration. The aim of the present report is to point to the possible concurrent role of two pathogenetic mechanisms in the same disease over a certain period of time, which resulted in severe disability in our patient.

CASE REPORT

In May 2004, a 56-year-old woman presented to the Department of Ophthalmology for visual impairment and blepharoptosis accompanied by edema of the eyelid and diplopia. In November 2003, the patient was diagnosed with myelodysplasia, refractory anemia subtype with blast eruption. From the diagnosis, the symptomatology mostly included intermittent edema of the joints (knee and wrist) and auricles, yet the patient received no therapy. Ophthalmologic examination showed blepharoptosis accompanied by swelling and conjunctival chemosis with pronounced proptosis (6mm). Eye movements were restricted in all directions. Visual acuity with maximal correction was 0.5 and 0.7 in the right and left eye, respectively. Funduscopy revealed unsharply delineated nasal margin of the optic nerve papilla on the right and normal finding on the left side. On admission, reaction to light was present but very sluggish. Orbital CT showed bilateral optic nerve thickening (0.54 cm and 0.53 cm orbital diameters on the right and left side, respectively), and a high-density lesion of the retrobulbar space on the right (optic nerve diameter increases from about 0.16 cm within the eye, to 0.35 cm in the orbit to 0.45 mm within the cranial space) (Fig. 1). The finding was verified by NMR analysis, suggesting the same mechanism, although cell infiltration could not be demonstrated without histopathologic analysis. Infective agents were ruled out. Then, the patient was for the first time prescribed low dose cytosine arabinoside, which resulted in regression of ptosis and proptosis after 4-week therapy, however, amaurosis developed in the right

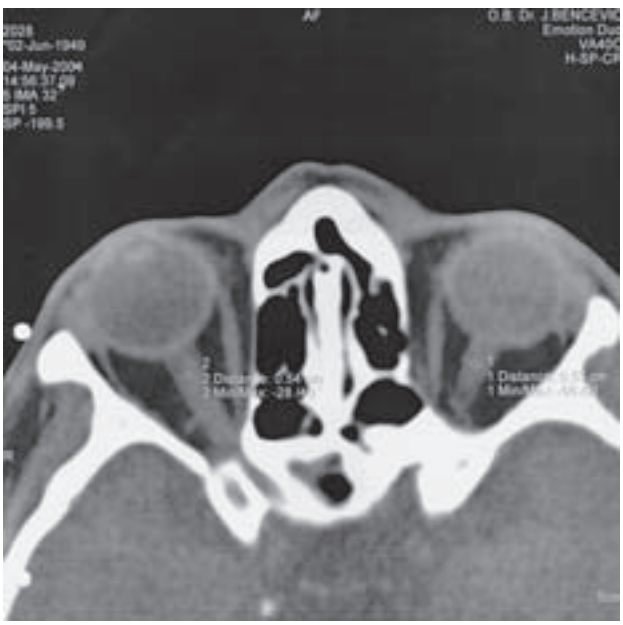

Figure 1. Orbit CT: bilateral optic nerve thickening.

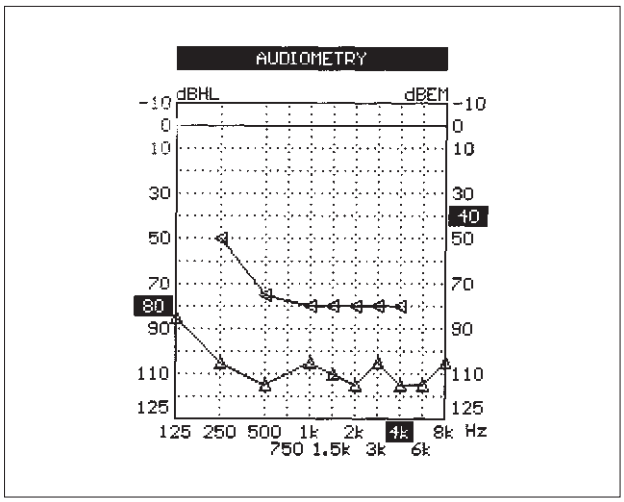

Figure 2. Acute sensorineural hearing loss in the right ear.

eye. At the same time, before the first cycle of chemotherapy, the patient developed acute hearing loss in the right ear, with attacks of swerving to the right. Oropharyngoscopy, rhinoscopy, otoscopy, laryngoscopy and palpation of the head showed normal findings. Audiology indicated sensorineural hearing loss in the right ear and normal hearing in the left ear. Tympanometry produced normal finding, whereas cochleostapedial answers were absent on the right ear. Hearing examination was applied by AMPLAID 319 and AMPLAID A756 devices. Cranial nerve findings were normal, except for the optic nerve. There was no spontaneous nystagmus and no overt lateralization on the Romberg test; electronystagmography showed already compensated disproportion of the right vestibular sense, while the results of vestibular tests of NASA R-93 type were uncertain due to the locomotor system affection. Auditory brainstem potentialis (ABR) showed extended latency of wave I (without change in amplitude) and extended interwave latency I-III. CT and nuclear magnetic resonance (NMR) of the ear produced normal findings. At ENT Department, the patient received parenteral therapy consisting of vasodilators, corticosteroids and spasmolytics; however, instead of recovery the patient developed complete hearing loss (the audiometer has protective limitation on the bone examination over 50 to 80 dB) (Fig. 2). At the beginning of July 2004, the patient was readmitted to the Department of Ophthalmology for disturbances in the left eye, which fully corresponded to those ob-

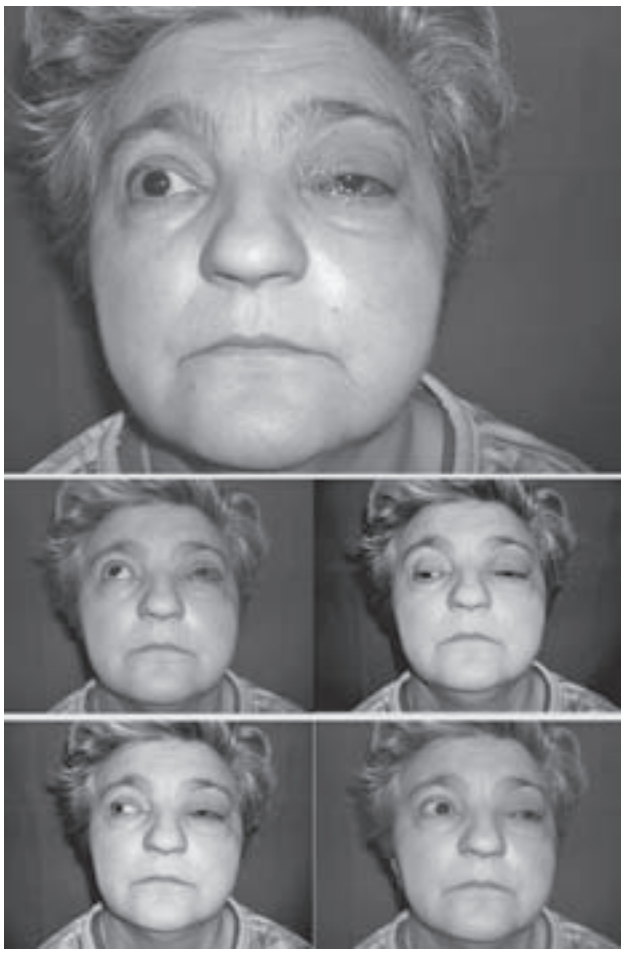

Figure 3. Proptosis and chemosis of the left eye conjunctiva. Limited bulbar motoricity.

served in the right eye two months before, and associated with severe conjunctival chemosis (Fig 3). The patient was on continuous therapy with low dose cytosine arabinoside. In one-month period, the clinical picture showed no regression while visual acuity dropped to zero. Visual evoked potentials (VEP) were without response. On funduscopy, bilateral paleness of the optic nerve papillae and overt optic nerve atrophy on the right, with bilateral presence of relative afferent pupillary defect (RAPD) were observed. Upon completion of ocular impairment, the patient reported tinnitus in the left ear accompanied by hearing loss that gradually progressed, however, without vertigo. Hearing threshold ranged first between 45, 20 and 55 dB, at one month between 50, 70 and 110 dB (Fig 4), up to total hearing loss at 3 months.

The patient died in 2005.

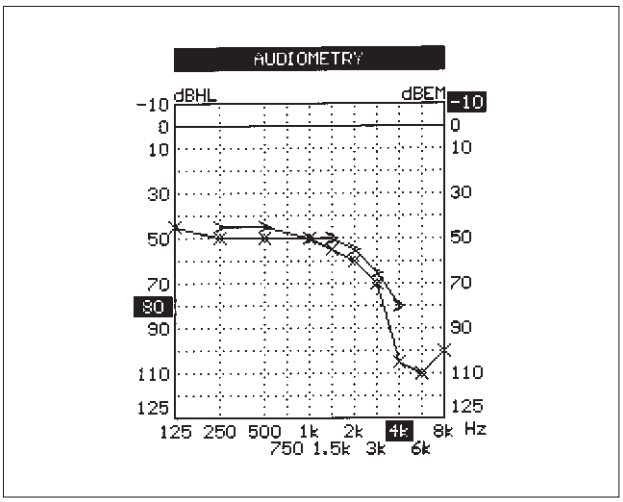

Figure 4. Abrupt sensorineural hearing loss in the left ear.

Histopathology evidence of temporal bone also could not be demonstrated because the patient's family did not allow the autopsy.

Eventually, the patient developed bilateral amaurosis and deafness, associated with persistent polymorphic disorders varying from month to month, such as edema of the auricles, knees and ankles, and headaches, additionally restricting her mobility and social contacts. Changes in leukocyte count, platelet count and erythrocyte sedimentation rate were as variable as the clinical picture (Fig 5).

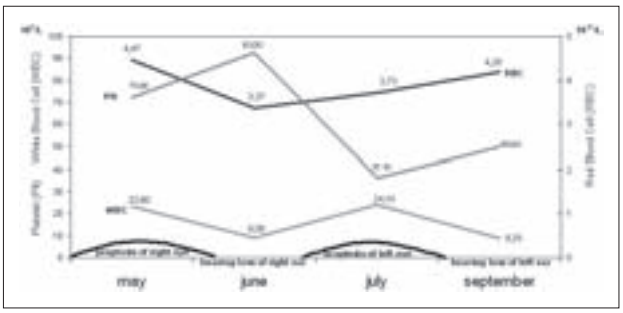

Figure 5. Clinical pattern of audiologic, ophthalmologic and main biochemical parameters.

DISCUSSION

In MDS, the time elapsed from the onset of symptoms to the diagnosis ranges from 0 to 23 months, median 2 months. MDS patients may be free from symptoms; then the diagnosis is mostly made by routine blood tests. The others experience fatigue and paleness due to anemia, systemic bacterial or fungal infections, prolonged temperature elevation, bleeding and lymphadenopathy, found in less than 10% of MDS in adults. Intensive chemotherapy is useful for induction of bone marrow remission, but is of short-lived action; therefore relapse of the disease usually occurs in two years of initial remission (9). Cytosine arabinoside is a chemotherapeutic most commonly used in the treatment of this disease, now usually in combination with idarubicin, cyclophosphamide, fludarabine, topotecan, etc. (10, 11)

During the course of disease, our MDS patient developed hearing loss and blindness before the first cycle of chemotherapy. This case implied a very intriguing pathogenesis, as MDS symptomatology was primarily associated with leukemic cell infiltration (4).

Audiologic examination confirmed hearing loss in the right ear and raised suspicion of vestibular nerve affection. CT and NMR of the ear showed no pathologic changes in the area of temporal bone pyramids, thus excluding the mechanism of leukemic cell infiltration. Loeffler and Mclean describe bilateral necrotizing scleritis and blindness in MDS as sequels of RPC (2). RPC is a rare disease of unknown etiology, characterized by recurrent inflammation of cartilage and fibrous tissue, with a high rate of ear and eye involvement. The disorder has been associated with HLA-DR4 and results from the action of autoantibodies upon collagen that leads to a reduced amount of proteoglycans in the cartilage. RPC is one of the rare disorders that can cause a bilateral symmetrical audiovestibular lesion. Monolateral or bilateral auricular chondritis is most common (in 85% and 40% of cases, respectively), followed by neurosensory hypoacusis and tinnitus (12). RPC is considered to be a paraneoplastic phenomenon of MDS (1). These authors explain scleritis and hearing loss by the same RPC mechanism, however, they could not apply it with certainty to blindness (they did not perform CT; on post mortem analysis they found no optic nerve thickening but observed retinal and choroid lesions); they are the only ones associating RPC with myelodysplasia. Ocular inflammation is present in 65% of cases (12), usually bilateral, with episcleritis and scleritis as the most common manifestations (13-16), followed by cataract, optic neuritis, and occlusion of the central vein of retina. In our patient, bilateral optic nerve

and retrobulbar tissue thickening strongly suggested leukemic cell infiltration, although RPC syndrome could not be excluded as the cause of blindness. As leukemic cell infiltration could not be demonstrated in the inner ear, the hearing loss and intermittent edema of the joints and auricles were attributed to RPC. The manifestation of RPC is not accompanied by laboratory abnormalities (1). In our patient, the acute onset of proptosis was accompanied by laboratory findings, which showed blood count deterioration, whereas blood tests performed during hearing impairment were nonspecific.

It should be noted that deficits were as severe and persistent before as during the administration of chemotherapy, thus precluding any hope for therapeutic efficacy. As corticosteroids are recommended for the treatment of RPC, the patient received them on several occasions, with a variable success; however, the overall therapeutic result was indicative of spontaneous regression with sequels, as in the episode of acute hearing loss in the right ear, which developed in spite of treatment with high doses of corticosteroid.

The heterogeneous clinical picture observed in our patient, also reported elsewhere, pointed to the as yet inadequately elucidated pathogenetic mechanism of MDS, and suggested at least two mechanisms to be involved, i.e. leukemic cell infiltration and RPC, acting concurrently in this case. Whether these two mechanisms are simply different forms of a single entity, or they stimulate each other, remains unknown. Clarification of this dilemma will certainly influence therapeutic approach.

Two years after MDS verification, our patient died deaf and blind, with frequently relapsing polymorphic defects, and unresponsive to any form of adjuvant therapy.

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