Literature Reviews

Ocular manifestations in patients with hematologic malignancies

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Ocular manifestations in patients with hematologic malignancies may develop either as a primary sign of the underlying disease or as relapse in remission. In addition, ocular involvement may result from anemia, thrombocytopenia, and coagulopathy, as well as infectious lesions caused by complications developing in the patient. Moreover, ocular toxicity may develop if the patient is treated with cytostatic and/or targeted agents. The review indicates that leukemia should be ruled out in the presence of ocular lesions (especially, hemorrhagic complications and retinal and optic nerve lesions). In addition, while examining a patient in remission after therapy for hematologic malignancy, recurrent hematologic malignancy should be ruled out in the presence of ocular manifestations. Moreover, a high index of suspicion for ocular toxicity should be maintained while examining a patient treated with either conventional cytostatics or target therapy, because any ocular lesions in this patient may be manifestations of ocular toxicity, and if so, the patient requires urgent intervention or discontinuation of the therapy for underlying disease.

Although traditionally considered uncommon in adult patients with leukemia [1], reports in recent years [2, 3, 4] have drawn attention to ophthalmic manifestations in these patients due to changes in treatment strategies [5, 6]. Five-year survival has increased for many hematologic malignancies in the 21st century. Ten and 20-year relative survival (RS) for patients with common hematologic malignancies, particularly, acute myeloid leukemia (AML) and chronic myeloid leukemia (CML), substantially increased in 2002–2006 and 2012–16. Ten year RS was >50% in 2012–16 for patients with chronic lymphoid leukemia (CLL), non-Hodgkin lymphoma (NHL), multiple myeloma (MM), and acute lymphoid leukemia (ALL). In addition, long survival times and recovery rates are expected to further increase for these patients [5]. It is important to note that there is a tendency to an improvement in therapeutic outcomes of elderly leukemia patients with numerous comorbidities, particularly, ocular disorders [6].

Recent studies [7-11] on epidemiology, diagnostics and treatment potential for ocular manifestations in patients with particular hematologic malignancies have found new features requiring further research and analysis to improve eye care to these individuals. First, there is need for generalization and analysis of the classification system, with not only noting the existence of a particular disorder, but with the potential for considering various etiologies for an ophthalmic lesion. Second, it is known [2, 3] that, in systemic leukemia, leukemic infiltration may develop in the presence of a primary ophthalmic lesion [7] or as a manifestation of disease relapse in complete remission [8, 9], potentially posing a diagnostic challenge for the ophthalmologist.

Although numerous studies noted that leukemic infiltration is more characteristic for AML and ALL, there have been reports on specific ophthalmic lesions as a primary manifestation of MM [10, 11].

In addition, ophthalmic complications may occur due to the development of anemia, thrombocytopenia, or hyperviscosity syndrome, which is rather characteristic for leukemias [2]. Development of various infectious complications in the presence of disease and its treatments may be attributed to the same type of lesions, and may cause the systemic or local immunodeficiency [12].

Anemia, thrombocytopenia, and coagulopathy with subsequent hypoxic and hemorrhagic ocular lesions can be conventionally considered as a polyetiologic phenomenon caused by the disease itself or its standardized treatments [2]. However, the use of cytostatic or immunobiologic agents might result in specific transient or permanent ocular manifestations with substantial deterioration of the quality of life during remission [13].

Let us consider the course, diagnostics and therapy of the ocular manifestations of hematologic malignancies.

Studies vary in the incidence of ocular manifestations of ALL, from 3% to 27% [4, 14]. Such discrepancies are likely to be caused by differences in patient's age and regional differences. The risk of ocular manifestations is high in patients (especially, in children) with ALL, but pediatric ALL patients treated with the use of current cytostatic treatment protocol (ALL-99) were 1.8 times less likely to develop these complications than those treated with the ALL-09 protocol. In addition, ocular hypertension was found the most prevalent ocular manifestation in pediatric ALL patients [14]. There have been reports of isolated cases [14] of leukemic infiltration of the optic nerve manifested as a disease relapse which was verified only by MRI.

There are the trade-offs between the type of malignant tumor and the site of ocular lesion. For example, T lymphoblastic lymphoma is similar to ALL with regard to cytologic and immunophenotypic characteristics, and the case of a girl with T lymphoblastic lymphoma relapse taking the form of isolated optic neuropathy has been reported [16]. However, in that case, the authors considered transconjunctival optic nerve biopsy (rather than MRI) as the major technique for diagnosing the disease. That is, verification of this type of ocular lesion in the presence of ALL requires further standardization.

Of note was the report that acute leukemia may present with serous retinal detachments without the signs of other retinopathy or ocular inflammation [17 16]. The researchers concluded that leukemia should be considered in the differential diagnosis of isolated serous retinal detachments. Retinal involvement is characteristic for numerous blood disorders [17], making the diagnosis a challenge for the ophthalmologist, and close cooperation between ophthalmologists and hematologists is required in order to meet this challenge. Those authors believe that the cases with poorly understood retinal changes with hemorrhages and petechiae require special attention and blood studies.

In a study from Pakistan [18], ophthalmic manifestations were present in 29 patients of AML (52.7%) and 18 patients of ALL (42.85%). Ocular involvement was significantly more common in newly diagnosed as compared with follow-up patients. Posterior segment was the most common site of ocular involvement (n=48, 49.5%) with retinal hemorrhages seen in 40 patients (41.2%) and papilloedema in seven cases (7.2%). Thirty-three (70.2%) out of 47 patients with ophthalmic manifestations were asymptomatic.

Ophthalmic manifestations were present in a substantially higher percentage (70%) of leukemia patients in a study from Nigeria [19] than in the above study, with the most common manifestations being intraretinal hemorrhage (31.3%) followed by retinal venous tortuosity (26.3%), roth spots (23.8%) and retinal infiltrates (21.3%).

In a study from India [4], ocular manifestations of leukemia were found in 51.9% of patients with acute leukemias. Primary or direct leukemic infiltration was seen in 8.3% of subjects while secondary or indirect involvement due to anemia, thrombocytopenia, hyperviscosity, total body irradiation, and immunosuppression were seen in 43.8% of subjects. In another study from India [20], among acute myeloid leukemia patients (23.5%), the presence of intraretinal hemorrhages was significantly associated with low Hb (Mann-Whitney U-test = 25.000, P = 0.007). The patients of acute lymphoblastic leukemia (25.4%) showed significant association between intraretinal hemorrhages and low platelet count (Mann-Whitney U-test = 44.000, P = 0.046).

In a study of the Danish population of patients with orbital/ocular manifestations of acute leukemia [21], of the nine patients [21], four had B-cell precursor acute lymphoblastic leukemia and five had AML. Common symptoms were proptosis, displacement of the eye, and reduced eye mobility in patients with orbital leukemias and pain, and reduced visual acuity in patients with ocular leukemias. All but one patient with secondary ophthalmic manifestations died of relapse/disseminated disease. Genomic profiling revealed that leukemias with and without ophthalmic manifestations had similar immunophenotypes, translocations/ gene fusions and copy number alterations.

In a large-scale nationwide Japanese survey of adult T-cell leukemia/lymphoma-related ocular manifestations [22], common ATL-related ocular lesions were intraocular infiltration (22 cases, 45.8%) and opportunistic infections (19 cases, 39.6%). All cases of opportunistic infection were cytomegalovirus retinitis. Dry eye (6.3%), scleritis (4.2%), uveitis (2.1%), and anemic retinopathy (2.1%) were also seen.

There has been described a case of relapsed pediatric acute lymphoblastic leukemia which initially presented as acute open angle glaucoma in the right eye [23]. B-scan ultrasonography suggested total retinal detachment. Eight weeks later, based on routine cerebrospinal fluid analysis, the patient was diagnosed with central nervous system relapse of T-cell ALL. Repeat B-scan 1 week later showed a new hyperechoic subretinal mass. Fine needle aspiration of the mass confirmed leukemic infiltrate. The involved eye was enucleated, demonstrating leukemic cells throughout the subretinal space, choroid, and the optic nerve. Following hematopoietic stem cell transplant, the patient continued to maintain bone marrow remission 5 months after enucleation without involvement in the opposite eye. Those authors concluded that retinal detachment in any patient with a history of leukemia should raise the possibility of relapse and may warrant aspiration/biopsy if other means of diagnosing relapse are inconclusive. In addition, subretinal infiltrate may progress rapidly and prompt diagnosis is paramount to tailoring therapy and preserving vision.

In a retrospective evaluation of a group of 67 patients with acute leukemia examined at the Ophthalmology Clinic, Faculty Hospital Ostrava, from 2005 to 2014 [24], ocular pathological findings were found in 13 patients of

the group (19.4 %) - 7 patients with AML (10.9 %) and 6 patients with ALL (8.5 %). Ten patients died due to of the underlying disease. Ocular pathological findings were found in 6 of them (60 %). A higher prognostic value was found in a group of patients with AML.

Of note that, in the last decade, there has been no reports on ocular manifestations of acute leukemia in a Ukrainian population, and these manifestations may have specific features and clinical and diagnostic aspects.

Ocular manifestations in chronic leukemia are significantly less common than in acute leukemia. In an Indian study [25], intraocular manifestations were noted in 7.7% patients of chronic leukemia, and were associated with severe anemia, leukocytosis and thrombocytopenia. The most common clinical manifestation was intraretinal hemorrhages. In another Indian study [4], the ocular manifestations were significantly (P = 0.01158) more frequent in myeloid leukemias (52.9%) than in lymphoid leukemias (28.6%). In addition, all the primary leukemic manifestations were seen in males.

In a systematic review of articles describing CLL ophthalmic involvement [26], there were 86 articles describing 123 cases of patients with ophthalmic involvement associated with CLL, and ophthalmic symptoms were CLL's first manifestation in 25.6% of patients. There were three main causes of ophthalmic features: CLL-infiltration (52.0%), lymphoma (26.0%), and infection (15.4%), with specific clinical and radiological characteristics. CLL-infiltration was mostly bilateral, whereas lymphoma was usually unilateral (P = 0.02). Optic neuropathy was always secondary to CLL-infiltration, and in those cases, cerebrospinal fluid immunophenotyping was a potential alternative to invasive biopsy. On the contrary, lymphoma usually presented as adnexal involvement (P = 0.04), particularly as an orbital mass (P = 0.004). Infections concerned mostly patients previously treated for CLL (P < 0.0001), and main presentations included posterior uveitis (P = 0.0002) and retinal infiltrates (P < 0.0001). Overall, the prognosis was poor, as 29.3% of the patients died within 36 months of follow-up, and 26.1% had a partial or total visual loss. Eye infections were associated with the poorest prognosis as 47% of patients died, with a 6-month-median survival.

In multiple myeloma, plasmacytomas can present as a solitary tumor, as an initial sign of systemic disease, or as a disease relapse. A study [9] presented 3 cases in which epibulbar, orbital, and iridociliary plasmacytoma with secondary glaucoma were presenting signs of uncontrolled multiple myeloma.

The presence of retinal vasculopathy in the absence of typical predisposing factors should suggest a possible underlying hematologic abnormality [27]. In such cases, a systemic investigation may reveal a potentially fatal hypercoagulability or hyperviscosity syndrome. Retinal vein occlusion is the most commonly encountered ophthalmic finding in such syndromes; however, abnormalities of the arterial system, the choroid, and the macula are also possible. Visual symptoms may be the only manifestation of the underlying process, making timely diagnosis by the ophthalmologist critical for both treatment and thrombotic prophylaxis.

Optic nerve lesions in patients with leukemia should be paid special attention. Yoshida-Hata and colleagues [28] reported the ocular findings in patients with hematopoietic malignancy with optic nerve involvement and abducens nerve palsy. Among the 8 patients, there were 3 cases of MM, 1 case of ALL, 1 case of follicular lymphoma, and 3 cases of AIDS-related lymphoma. Six cases had optic nerve invasion, 2 cases had abducens nerve palsy, and 1 case had optic nerve invasion of both eyes. The median visual acuity of eyes with optic nerve invasion was 0.885 logarithm of the minimum angle of resolution (logMAR) units. The final visual acuity of eyes with optic nerve invasion was 1.25 logMAR units, and that of those with sixth-nerve palsy was -0.1 logMAR units. Six cases died during the five-year follow-up period. An ophthalmic involvement in patients with hematopoietic cancer was associated with poor prognosis.

Saffra and colleagues [29] presented a case of recurrent MM of a patient who had been in disease remission. The patient presented with new-onset diplopia and an abduction deficit of the right eye, with mild proptosis. The orbital MRI demonstrated an isolated finding of eccentric enlargement of the right lateral rectus muscle. Chemotherapy was initiated, followed by orbital radiation and stem-cell transplantation for coexisting systemic disease. The orbital symptoms of proptosis and diplopia resolved within 1 month of treatment.

The venous congestion is considered to be the main clinical sign that occurs during the initial stage of leukemia, whereas white-centered hemorrhages are the most typical manifestations in leukemic retinopathy [30]. These complications usually manifest when the disease presents with clinical and hematological symptoms. Lyu and colleagues [30] reported a patient who was diagnosed with leukemic retinopathy. The initial signs of this disease were bilateral hemorrhages that occurred beneath the internal limiting membrane during complete clinical remission. In addition, flame-shaped hemorrhages were observed surrounding the optic discs and/or along the vessels in the absence of venous congestion. All these changes were present during complete clinical remission. Clinical remission was achieved following effective systemic chemotherapy that was applied for leukemia in the hematology department. Best-corrected visual acuity improved in the absence of surgery and/or medical treatment for ophthalmologic treatment.

A similar case was reported by Chaabani and Doulami [31] from Tunis. A patient who was hospitalized for pulmonary infection presented a brutal and bilateral reduced vision. The examination of eye fundus found white-centered retinal hemorrhages. The etiological assessment confirmed the diagnosis of acute leukemia. A treatment based on chemotherapy allowed a complete

remission. White-centered retinal hemorrhage is rarely revealing acute leukemias. Acute leukemia is one of the most serious etiologies. Those authors believe that hematologic malignancies should be ruled out in the presence of retinal hemorrhages, because they are the most dangerous among possible disorders. They concluded that a complete ophthalmological examination and a serious and wide etiological investigation are needed to help the discovery of white-centered retinal hemorrhage, with acute leukemia being one of the most serious etiologies.

Ocular toxicity is an important factor of ocular lesions in patients with hematologic malignancies treated with cytostatics, and has been reported to occur with initiation of systemic therapy [12]. In addition, it remains a major hurdle in the implementation of many of the targeted anticancer drugs [32]. Ocular complications induced by cytotoxic chemotherapy may be categorized as reversible or irreversible, and acute or chronic disorders. Mild and moderate ocular complications are rather common and they are reversible with cessation of cytostatic therapy. Some manifestations of ocular toxicity may require a reduction in the dose or cessation of cytotoxic chemotherapy in order to prevent vision loss [33]. If the signs of ocular toxicity are early recognized, ocular toxicity may be treated and even prevented. Routine eye examination should be performed for patients receiving cytosine arabinoside, 5-fluororacil, methotrexate or docetaxel [34].

It is noteworthy the issue of ocular toxicity is especially challenging in topical cytostatic therapy for malignancies. The ocular manifestation of 12 patients with ocular leukemia and the result of their treatment with intravitreal methotrexate (MTX) injections have been reported in a study by Vishnevskia-Dai and colleagues [35]. The 12 patients included 7 women and 5 men. Eleven eyes of 6 patients were treated with intravitreal MTX injections. The indication for treatment was biopsy proven, tumor cell infltration. The mean number of MTX injections was 3.37 ± 5.35 (range 1–18). The mean follow-up was 27.08 ± 36.79 months (range 1–93). All treated eyes showed improvement in the infammatory reaction and tumor cell infltration. Vishnevskia-Dai and colleagues found that Intravitreal MTX injections may be an effective therapeutic approach for eyes with intraocular leukemic tumor cell infiltration. No patient in that study developed side effects from the injections.

The advent of novel targeted agents for leukemia did not solve the problem of ocular toxicity of therapeutic agents, and further research on diagnostic and treatment measures for patients with leukemia is still required. Roop and colleagues [36] reported a case of a diabetic with diabetic retinopathy and medically uncontrolled neovascular glaucoma (NVG) who underwent intracameral bevacizumab followed by trabeculectomy. Following imatinib therapy, there was a rapid progression and recurrence of neovascularization, eventually leading to failure of trabeculectomy OD and bilateral severe loss of vision. Imatinib may be implicated in the worsening of NVG in CML patients, especially with co-existing diabetes and thus, such patients should receive regular thorough ophthalmic evaluation as long as imatinib continues.

Several cases of differentiation syndrome presenting with ocular manifestations in patients with acute promyelocytic leukemia treated with all-trans retinoic acid have been reported [37, 38]. Newman and colleagues [38] described two cases with bilateral reduction in visual acuity at days fourteen and ten respectively following initiation of differentiation therapy in addition to developing other systemic manifestations of differentiation syndrome. Both patients received the same chemotherapeutic regimen including both all-trans retinoic acid and arsenic trioxide as well as ten days of routine differentiation syndrome prophylaxis with oral prednisolone. Common to both presentations was the presence of bilateral reduction in visual acuity with multifocal serous retinal detachment secondary to chorioretinopathy. The visual outcome from both presentations was excellent with rapid normalization of visual acuity and resolution of the sub-retinal fluid with only the first case having their differentiation therapy temporarily withheld during the acute phase of illness.

Monoclonal antibodies are believed to be more specific and less toxic than conventional cytotoxic therapy, but they were found to be associated with various toxicities such as ocular toxicity. Many of the molecules targeted by anticancer agents are also expressed in ocular tissues. Ocular toxicity was described for many adopted targeted agents and several classes of agents that are currently undergoing phase 1 or 2 clinical trials [39]. Non-specific inflammation is involved in the pathogenesis of these complications. Continuous cooperation between oncologists and specialists in eye diseases is essential because molecularly targeted agents have been increasingly used, and novel targeted combinations of agents are being developed.

A retrospective case series [12] reported the ocular side effects of traditional and novel chemotherapeutic agents from a large center. Of the 161 oncology patients referred to the ophthalmology clinic for chemotherapeutic screening or ocular side effect, 31 (19.3%) were identified as having an ocular adverse reaction due to a novel or traditional chemotherapeutic medication. The most frequent medication with ocular toxicity was interferon-α(2b) (IFN-α(2b)) (6/31, 19.4%); headache was typical in these patients (83.3%). Ibrutinib ocular toxicity was second most common (5/31, 16.1%), usually causing red or dry eye, while one patient developed branch retinal artery occlusion. Retinal abnormalities documented on OCT imaging occurred with IFN-α(2b), ipilimumab, binimetinib, and docetaxel. Inflammatory conditions included anterior scleritis with zoledronic acid, focal eyelid inflammation with veliparib, bilateral chemosis with R-CHOP, iritis, and blepharospasm with IFN-α(2b). Two patients (2/31, 6.5%) developed permanent vision loss. Six patients were lost to follow-up, and the clinical course was unknown (6/31, 19.4%).

In a recent review on ocular adverse events (AEs) associated with antibody-drug conjugates in human clinical trials [40], it was concluded that the most commonly reported AEs involved the ocular surface and most ocular AEs were not severe (≤ grade 2). In addition, clinical outcomes were not consistently reported, but when specified, most AEs improved or resolved with cessation of treatment or with ameliorative therapy. The toxicologic mechanism(s) and pathogenesis of such events are not well understood, but most are mild in severity and reversible. Drug development and medical professionals should be aware of the clinical features of these events to facilitate early recognition and intervention in the assessment of preclinical development programs and in human clinical trials. Further research is required to elucidate the prevalence and pathophysiology of these side effects and to improve the quality of life of patients.

Summing up this short review of ophthalmic manifestations in adult patients with hematologic malignancies, leukemia should be ruled out in the presence of ocular lesions (especially, hemorrhagic complications and retinal and optic nerve lesions). In addition, while examining a patient in remission after therapy for hematologic malignancy, recurrent hematologic malignancy should be ruled out in the presence of any ocular manifestations. Moreover, a high index of suspicion for ocular toxicity should be maintained while examining a patient treated with conventional cytostatics or target therapy, because any ocular lesions in this patient may be manifestations of ocular toxicity, and if so, the patient requires urgent intervention or discontinuation of the therapy for underlying disease.

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