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·专家述评·

需加强对眼内淋巴瘤的重视

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[摘　要]　眼内淋巴瘤(intraocular lymphoma，IOL)比较罕见。按起源位置分为两种类型，主要类型为原发性眼内淋巴瘤(primary intraocular lymphoma，PIOL)，也称为原发性中枢神经系统淋巴瘤(primary central nervous system lymphoma，PCNSL)；另外一种类型为继发性眼内淋巴瘤(secondary intraocular lymphoma，SIOL)，为中枢神经系统以外的淋巴瘤转移至眼内。按肿瘤类型主要分为三类，主要类型为眼内弥漫大B细胞淋巴瘤，属于高级别淋巴瘤，预后较差；其次为少见的主要侵犯脉络膜的黏膜相关淋巴组织结外边缘区B细胞淋巴瘤，属于低级别淋巴瘤，预后较好；第三种类型为极少见的眼内NK/T细胞淋巴瘤，属于高级别淋巴瘤，预后极差。该病的诊断对眼科医生和病理医生都极具挑战性。实验室检测方法主要包括病理学、免疫细胞化学、流式细胞术、细胞因子及基因重排等，但眼内病理活检仍然是该病诊断的金标准。该病的治疗主要为眼内局部化疗、放射治疗及系统性化疗。IOL早期常因误诊而耽误治疗，目前该病明确诊断时多在患者出现症状后4~40个月，多数病例早期被误诊为葡萄膜炎而失去治疗的最佳时机，导致预后较差。因此应充分认识IOL的早期表现，早期诊断、早期治疗，从而大大提高疗效。

[关键词]　眼内淋巴瘤；诊断；治疗

Attention should be paid to intraocular lymphoma

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Abstract　Intraocular lymphomas (IOL) are rare malignant neoplasms including primary intraocular lymphoma (PIOL) and secondary intraocular lymphoma (SIOL). The former is also known as primary central nervous system lymphoma (PCNSL). The latter is a kind of lymphoma metastasizing to the eye from outside the central nervous system. IOL can further be divided into three different types. The most common type is vitreoretinal high-grade diffuse large B-cell lymphoma with poor prognosis. The less common type is primary choroidal extranodal marginal zone B-cell lymphoma of mucosa associated lymphoid tissue, which is low-grade B-cell lymphoma with better prognosis. The rare type is NK/T cell lymphomas with very poor prognosis. The diagnosis of this disease is challenging for both ophthalmologists and pathologists. Laboratory testing methods mainly include cytology/pathology,

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immunocytochemistry, flow cytometry, cytokine analysis and gene rearrangement detection. The detection of malignant lymphoid cells cytologically/pathologically is still the gold standard for diagnosing IOL. The treatment involves local chemotherapy, radiotherapy and systemic chemotherapy. Most intraocular lymphomas at early stage are misdiagnosed as uveitis and proper treatment is often delayed with poor diagnosis due to the lost of best time for treatment. So far, the delay between the diagnosis and the onset of ocular symptoms ranges from 4 to 40 months. Therefore, we should fully understand the early manifestations of intraocular lymphoma and early diagnose and timely treat the disease in order to improve prognosis.

Keywords intraocular lymphoma; diagnosis; treatment

眼内淋巴瘤(intraocular lymphomas，IOL)是一种较罕见的眼内恶性肿瘤，近几年发病率逐渐增加[1-3]。其临床表现非常复杂，早期常常被误诊为眼内炎而延误治疗，导致预后较差[1,3]。所以我们应该充分认识IOL的临床特征，使患者能够得到及时诊断和治疗，从而提高疗效。

1 流行病学

IOL的发病率约占眼内恶性肿瘤的1.86%。近几年由于免疫缺陷、免疫力低下患者的增加，寿命的延长及诊断手段的提高，IOL的发病率在逐渐增加，在美国估计每年有300~380例新发病例[1-3]。该病好发年龄为50~60岁，但也可发生于婴幼儿和青少年[4-5]。初发时可为单眼或双眼病变，但80%~90%的患者最终发展为双眼病变[1]。先发生IOL的患者有56%~90%通常在29个月内发生颅内病变[1]。先发生颅内淋巴瘤的患者有15%~25%会发生眼部病变[1]。该病好发于女性，男女发病率约为1:2[6-8]。但也有男性发病多于女性的报道[9]。该病发病率没有人种差异[9-10]。

2 病因学

IOL的致病原因仍然不清楚。免疫力低下、EB病毒感染、弓浆虫感染等都可能与该病有关[11-13]。感染性抗原所驱动的B淋巴细胞的扩增，然后转变成克隆性扩增有可能是该病的始发因素[14]。总之，遗传、免疫、微环境因素都可能导致该病的发生[15]。

3 临床特征

原发性眼内淋巴瘤(primary intraocular lymphoma，PIOL)最常见的类型是原发性眼内弥漫大B细胞淋巴瘤，是原发性中枢神经系统淋巴瘤(primary central nervous system lymphoma，PCNSL)的亚类[1-3]。该病恶性度高，通常伪装为双眼非特异性葡萄膜炎和玻璃体炎，甚至对糖皮质激素治疗有反应，使得诊断变得困难[1-3]。双眼发病约占64%~83%[16]。临床表现常常为视物模糊、视力下降、眼前黑影漂浮等[17]。超过50%的患者有明显的玻璃体混浊，裂隙灯下呈白色颗粒状、片状和团块状，眼底镜可见视网膜下大小不一的黄白色病灶，导致视力下降[1,18]。偶然会发生玻璃体后脱离和玻璃体出血[19]，及急性视网膜坏死、视网膜血管炎，渗出性视网膜脱离等[17]。而眼前段一般无异常。有时该病可以表现为双眼肉芽肿性全葡萄膜炎[20]。如果发生颅内侵犯，有可能发生行为改变和认知功能障碍[21]。光学相干断层扫描(optical coherence tomography，OCT)检查在视网膜色素上皮下可见点状及结节状高反射病变[22-24]。在眼底自发荧光方面，高荧光点对应于视网膜色素上皮下的淋巴瘤细胞浸润灶，低荧光区对应于淋巴瘤细胞导致的色素上皮萎缩区[1,25]。荧光造影可见小病灶表现为早期荧光遮蔽，中晚期荧光着染，大病灶早晚期均为荧光遮蔽[24,26-28]。少数会出现炎症表现，如血管渗漏、黄斑囊样水肿、视乳头渗漏[1]。

眼内原发性黏膜相关淋巴组织(mucosa-associated lymphoid tissue，MALT)淋巴瘤，即结外边缘区B细胞性淋巴瘤，是一种惰性淋巴瘤，目前发现的病例病变均位于葡萄膜组织，多数在脉络膜[29-30]。多见于50岁以上男性，多数单眼发病，少数累及双眼[30-31]。典型症状包括反复发作的视物模糊，以及继发于黄斑部浆液性视网膜脱离的视物变形。视力逐渐下降，脉络膜增厚、渗出性视网膜脱离，少数患者表现为眼内葡萄膜炎[29-31]。早期可能

对糖皮质激素治疗敏感，最终葡萄膜弥漫增厚，约50%患者会通过巩膜隧道扩散至眼球外[29-32]。

眼内T细胞淋巴瘤很少见，主要为NK/T细胞淋巴瘤，大部分是中枢神经系统以外的淋巴瘤转移至眼内[33]。由于NK/T细胞淋巴瘤往往有较多瘤细胞坏死，临床上常常表现为眼红、眼痛、眼内脓样物质，类似感染性眼内炎的表现[34]。原发性眼内NK/T细胞淋巴瘤极罕见，可以侵犯视网膜、虹膜、睫状体、脉络膜，侵犯视网膜者临床表现类似眼内弥漫大B细胞性淋巴瘤[35]。其他少见的眼部表现包括炎症性青光眼、完全性瞳孔散大、脉络膜脱离等[36]。原发性病变最常见部位是皮肤，同时中枢神经受累约占31%[37]。

磁共振检查常常能很好地显示颅内病变，病变在平扫T1WI表现为低信号，T2加权通常表现为等强度到低强度信号，病变周围显示不同程度水肿[38-39]。

4 实验室检查

IOL早期常因误诊而耽误治疗，目前该病明确诊断时多在患者出现症状后4至40个月[10,16,40]。IOL的检查手段包括病理形态学、免疫细胞化学、流式细胞术、炎症因子、基因重排等方法。病理活检仍然是IOL诊断的金标准[41-42]。形态上，典型的B细胞淋巴瘤细胞常常是细胞核增大、细胞质少，核质比增大，细胞圆形、椭圆形、不规则形，染色质粗，核仁明显或多个核仁[43-44]。免疫组织化学染色显示，B细胞淋巴瘤异型淋巴细胞CD20、CD79α阳性，CD3、CD5阴性。T细胞淋巴瘤，瘤细胞中等大小至细胞较大，细胞核异型明显。免疫组织化学显示瘤细胞CD3阳性，CD20、CD79α阴性。Ki-67增殖指数高，平均大于80%。可以通过细针穿刺或玻璃体切割获取标本，如果标本内细胞太少或细胞形态不典型，需要重新取材或取组织块活检。眼内液体要尽快送检，以免细胞变性，影响诊断[43-44]。送检液体细胞量太少，反应性T淋巴细胞及坏死细胞、晶状体纤维等均使诊断困难，是误诊的常见原因，所以最好行玻璃体切除术，尽量多收集瘤细胞，同时避免混入晶状体纤维，必要时行视网膜或脉络膜组织活检[41,43,45-46]。

检测眼内液体细胞因子有助于鉴别炎症和肿瘤。通常IL-6由炎症细胞产生，IL-10由B细胞淋巴瘤产生。玻璃体内IL-10浓度高于100 pg/mL和前房内IL-10浓度高于70 pg/mL，及IL-10/IL-6>1均高度提示原发性B细胞性IOL可能[17,47-49]。但当眼内弥漫大B淋巴瘤伴发眼内炎症反应时，情况就变得复杂，可能会出现假阴性结果[1,17]。玻璃体标本的流式细胞学检查是IOL的辅助检查方法，但炎症细胞及坏死细胞太多也会出现假阴性，且细胞数量过少也无法检测[1]。基因重排是IOL的另一种辅助检查方法，主要表现为IgH、IgK及IgL重链重排，眼内弥漫大B细胞淋巴瘤IgH基因重排率为80.6%[17]，眼内T细胞淋巴瘤TCR基因重排率为100%[14]。但是，由于炎症细胞及坏死细胞的干扰可能会出现假阴性及假阳性，且同样要求有一定的细胞数量[14,17]。

近年来MYD88基因突变的检测开始运用于IOL的诊断，其检测的敏感性为90.5%，在MYD88基因突变的眼内弥漫大B细胞淋巴瘤中，95%具有经典的L265P[50-51]；这种检测方法所需标本量少，眼内炎症对其检测影响较小，前景可期[52]。研究人员发现55% (40/72)的PIOL患者有bcl-2 t(14;18)异位[53]。眼内液体EB病毒的检测则有助于眼内NK/T细胞淋巴瘤的诊断[54]。

5 治疗

由于IOL发病较少，无法进行规范的队列研究，尚未形成标准统一的最佳治疗方案。治疗方式包括玻璃体腔内化疗、全身化疗、放疗，根据病变程度、累及范围，有无累及中枢神经系统，及患者身体状况选择单独或联合应用[55]。目前推荐的治疗方法是没有累及中枢神经系统及全身的局限性IOL可选择局部治疗，包括眼内注射甲氨蝶呤(4 g/L)和/或利妥昔单抗及眼部放疗[21]。眼部放疗加预防性中枢神经系统治疗可用于控制眼内病变，保持视力，阻止中枢神经系统累及[11]。外放射剂量30~50 Gy不等，平均约40 Gy[18]。放射治疗并发症包括放射性视网膜病变、玻璃体出血、干眼、结膜炎、新生血管性青光眼、视神经萎缩、白内障等[18]。对于累及中枢神经系统的患者，必须联合放疗和化疗[39,55-56]。美罗华是一种抗CD20的单克隆抗体，可以和甲氨蝶呤联合眼内注射以减少甲氨蝶呤注射次数及预防甲氨蝶呤耐药[57-59]。往往开始治疗效果很好，但随后复发需要玻璃体

腔内注射甲氨蝶呤及外放射联合治疗[57]。甲氨蝶呤可以单独使用，或同其他药物比如塞替派和地塞米松联合使用[27,60-62]。高剂量甲氨蝶呤是最有效的药物，单独使用时有效率可达72%，联合使用有效率可达94%~100%[63-64]。尽管开始治疗有效，但多次注射后会发生耐药[65]。对于复发性或有中枢神经系统累及的难治性PIOL，可行鞘内注射甲氨蝶呤和阿糖胞苷治疗[66]。对不同患者需进行个体化选择治疗方法。近年有II期临床研究[67]表明原发性中枢神经系统及IOL用雷利度胺联合眼内注射美罗华及甲氨蝶呤为基础的化疗作为一线治疗药物效果明显。

6 预后

文献[6,68-70]报道眼内B淋巴瘤的病死率为9%~81%，生存时间为12~35个月。由于患者较少，延迟诊断时间及治疗方法不同，报道的死亡率极不一致[68-70]。肿瘤复发很常见，有时治疗并不能阻止局部复发和中枢神经受累[68-70]。预后取决于以下几个方面：1)中枢神经系统是否受累。没有中枢神经系统受累的单纯眼部淋巴瘤往往预后较好。相反，有中枢神经系统受累的患者几乎短期内就会死亡[68-71]。神经影像学可以很好地显示是否有中枢神经系统受累[71-73]。2)组织病理学类型是另一重要因素。眼内MALT淋巴瘤对放疗敏感，治疗效果好，预后较好[30,68-70]。在一个系列报道中，对35例患者随访，其中有2例患者在8和20年后出现了系统性淋巴瘤，其余33例患者在3~20年随访中未出现全身病变[30]。眼内弥漫大B细胞淋巴瘤比T细胞淋巴瘤预后要好，眼内T细胞淋巴瘤预后极差，一般数月内死亡[33-35]。3)治疗时机。早期治疗预后较好[74]。原发中枢神经系统淋巴瘤，单独放疗或放疗加化疗患者平均生存时间为10~16个月[21]。4)复发性患者预后很差[75-76]。

7 总结

总之，IOL常常伪装成眼内炎症而导致误诊、误治及高病死率。对可疑IOL的患者应行眼内液体IL-10和IL-6细胞因子检测、细胞病理学检查、基因检测等，必要时取肿瘤组织块活检，以避免漏诊。IOL一旦确诊，要进行中枢神经系统的影像学检查以明确中枢神经系统是否受累。治疗手段包括放疗、玻璃体腔内注射化疗药物及系统性化疗等。由于已经确诊病变较少，尚需多中心研究来筛选最佳治疗方案，以提高预后。

开放获取声明

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