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Case Report

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The Immunosuppressant Tacrolimus-Induced Atypical Hyperplasia of Lymph Nodes: A Case Report

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Abstract

Background: Tacrolimus is a highly immunosuppressive drug, and its activity has been confirmed in vitro and in vivo experiments. This drug inhibits the production of cytotoxic lymphocytes and may induce lymph node atypical hyperplasia to some extent. It is necessary to diagnose, recognize, and distinguish the atypical hyperplasia, because nodular lymphocyte-dominated Hodgkin lymphoma is an indolent lymphoma that develops slowly and has a long survival period even if it recurs. The case was identified in diagnostic studies as proliferative lesions resembling nodular lymphocyte-predominant Hodgkin lymphoma, and a part of the reason was related to the child's long-term use of tacrolimus.

Methods: According to the patient's medical history data, systematic medication, pathological diagnosis, molecular testing, immunohistochemistry, physical examination, color ultrasound and a series of examinations, the patient is diagnosed as proliferative lesions.

Results: In this case, our diagnosis was considered atypical hyperplasia of lymph nodes indirectly caused by the pediatric patient's long-term use of the immune drug tacrolimus with a highly sensitive constitution.

Conclusion: The diagnosis suggests that proliferative lesions (resembling nodular lymphocyte-predominant Hodgkin lymphoma) are indirectly and probably caused by long-term use of the immune drug tacrolimus in pediatric patients with a hypersensitivity system. Early diagnosis can improve the survival of patients who are prone to relapse but have a longer survival even if they relapse.

Keywords: Tacrolimus; Nodular lymphocyte-predominant Hodgkin lymphoma; Diagnose; Atypical hyperplasia.

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Case presentation

A 10-year-old man was admitted to our hospital for a year after the discovery of a tumor in his neck. The boy had a history of eczema, a highly sensitive constitution, and a long history of taking the anti-immune drug tacrolimus.

Physical examination: an egg-sized lymph node can be touched on the right side of the neck, about 4 × 3 cm in size, medium, no tenderness, mobility can be, with no adhesions.

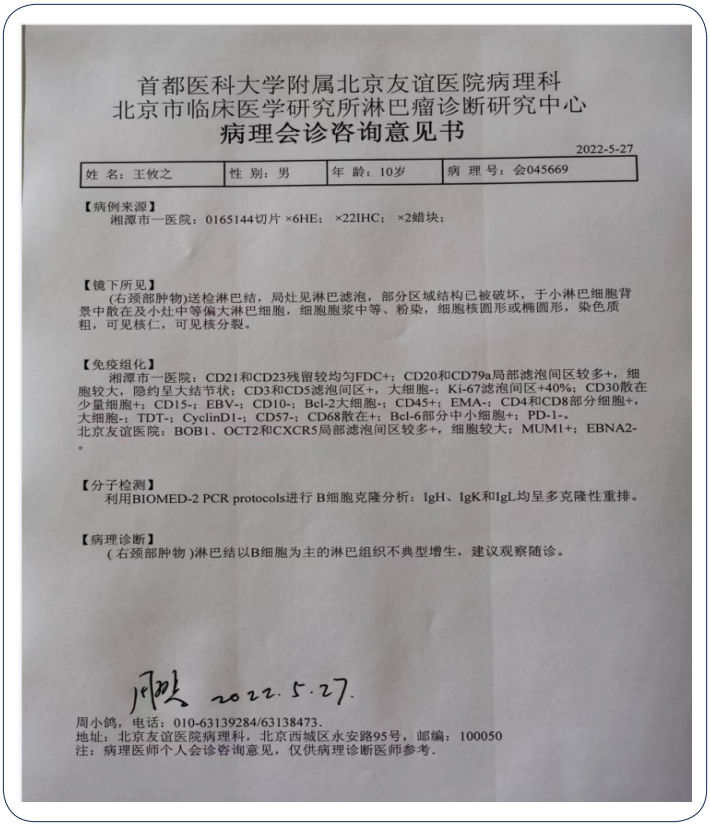
Color ultrasound: multiple nodules can be seen subcutaneously, some of which are a very low echo, oval, clear borders, enveloping, and internal echoes are under-clear.

Excision biopsy as seen by the naked eye: a round tumor, 4.5 × size 3 × 4 cm, gray, solid, local bleeding, delicate texture.

Microscopic: lymph nodes (right neck mass)are tested, lymph follicles are seen on focal spots, some regional structures have been destroyed, scattered in the background of small lymph node cells and medium-sized lymphocytes in small foci, the cytoplasm is medium, molten, nucleus is round or oval, coarse chromatin, the nucleoli are visible, the nuclear division is visible.

Immunohistochemistry: CD21 and CD3 residues are more uniform, FDC+; CD20 and CD79a local follicular zone more+, the cells are relatively large, vaguely large nodular; CD3 and CD5 follicular region +, large cells -; Ki-67 interveolar zone +40%; CD30 scattered in a small number of cells+; CD15-; EBV-; CD10-; Bcl-2 large cells-; CD45+; EMA-; CD4 and CD8 partial cells +, large cells -; TDT-; CyclinD1-; CD57-; CD68scattered+; Bcl-6 part of small cells +; PD-1-. BOB1, OCT2 and CXCR5 have more local follicular intervenorial regions and larger cells; MUM1+; EBNA2-.

Diagnosis: Proliferative lesions (resembling nodular lymphocyte-predominant Hodgkin lymphoma)



首都医科大学附属北京友谊医院病理科
北京市临床医学研究所淋巴瘤诊断研究中心
病理会诊咨询意见书

2022-5-27

姓 名：王牧之	性 别：男	年 龄：10岁	病 理 号：会045669

【病例来源】
湘潭市一医院：0165144切片 ×6HE； ×22IHC； ×2蜡块；

【镜下所见】
（右颈部肿物)送检淋巴结，局灶见淋巴滤泡，部分区域结构已被破坏，于小淋巴细胞背景中散在及小灶中等偏大淋巴细胞，细胞胞浆中等、粉染，细胞核圆形或椭圆形，染色质粗，可见核仁，可见核分裂。

【免疫组化】
湘潭市一医院：CD21和CD23残留较均匀FDC+；CD20和CD79a局部滤泡间区较多+，细胞较大，隐约呈大结节状；CD3和CD5滤泡间区+，大细胞-；Ki-67滤泡间区+40%；CD30散在少量细胞+；CD15-；EBV-；CD10-；Bcl-2大细胞-；CD45+；EMA-；CD4和CD8部分细胞+，大细胞-；TDT-；CyclinD1-；CD57-；CD68散在+；Bcl-6部分中小细胞+；PD-1-。
北京友谊医院：BOB1、OCT2和CXCR5局部滤泡间区较多+，细胞较大；MUM1+；EBNA2-。

【分子检测】
利用BIOMED-2 PCR protocols进行 B细胞克隆分析：IgH、IgK和IgL均呈多克隆性重排。

【病理诊断】
（右颈部肿物）淋巴结以B细胞为主的淋巴组织不典型增生，建议观察随诊。

2022.5.27.

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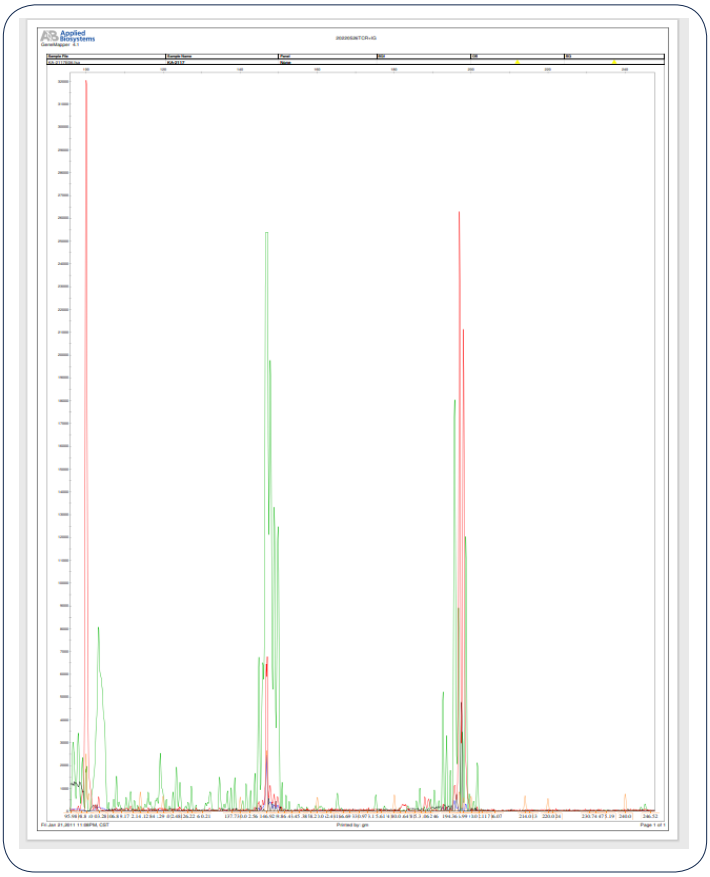
注：病理医师个人会诊咨询意见，仅供病理诊断医师参考。



Discussion

At the molecular level, tacrolimus is clearly useful for accumulation in cells using binding to a cellular protein (FKBP12). The FKBP12-tacrolimus complex specifically binds to and inhibits calcinurin, which inhibits the calcium-dependent signaling pathways produced in T cells, thus preventing transcription of discontinuous lymphogenemic genes [1]. This drug is a highly immunosuppressive drug, and its activity has been confirmed in vitro and in vivo experiments. This drug inhibits the production of cytotoxic lymphocytes that form the main transplant rejection effect. This drug inhibits the activation of T cells and the proliferative effect of T helper cells dependent on B cells. It also inhibits the production of lymphoid factors such as interleukin-2, interleukin-3, and γ-interferon and the expression of interleukin-2 receptors. At the molecular level, the effects of the drug appear to be produced by binding to a cellular protein (FKBP), which also causes the compound to accumulate between cells. In in vivo tests, the drug has been shown to be effective for liver and kidney transplantation [2].

Clinical experiments show that it has a good effect on heart, lung, intestine, and bone marrow transplantation [1,2,23,24]. FK506 also plays an active role in the treatment of Atopic Dermatitis (AD), Systemic Lupus Erythematosus (SLE), autoimmune eye diseases, myasthenia gravis, and other autoimmune diseases [25-27].

Atypical lymphoid hyperplasia refers to other malignant lesions in the lymph nodes that cannot be diagnosed as malignant lymphoma or lymphoid reticular tissue, and atypical hyperplasia of lymphoid tissue is benign and malignant lymphoid hyperplasia lesions that have not yet been determined, or lympho proliferative

lesions between typical hyperplasia and typical lymphoma [3]. At present, it can be classified as atypical hyperplasia of lymphoid tissue: lymphatic follicles have more than 5 hyperplasias of the same size and shape; Fusion and consistent hyperplasia of more than 1/3 of the lymph nodes in the paracortical region; Vascular immunoblastic lymphadenopathy; Proliferation of mucosal-associated lymphoid tissue in the focal consistent mononucleoid B-cell region; Extraosseous isolated plasma cell tumors; Pseudosymphima outside the node [4]. If the reactivity of lymphoid tissue is insufficient for the diagnostic criteria of lymphoma, but cannot be classified as reactive hyperplasia, in this case, it can be called atypical hyperplasia of lymphoid tissue, and its clinical significance is that such cases should be closely followed up because they may develop lymphoma.

According to the WHO classification, typical nodules are necessary for the diagnosis of this tumor. NLPHL may have diffuse areas [5,20]. CD20 staining is helpful for discrimination, Recognize nodules in diffuse areas. Looking for popcorn cells in nodules is diagnostic NLPHL is very important. There are many or few tumor cells. In this case, the tumor cells are rare and the tumor cells are relatively small, Misdiagnosis is easier when young. Follicular dendritic cells and germinal center cells in tumor cell body, It is difficult to identify in size, and the identification is mainly based on typical cell morphology and immunohistochemistry [6,7].

Based on previous case reports and literature studies, we have found that a small number of patients do have cancer after long-term treatment with tacrolimus, and tumorigenesis is likely [8].

Therefore, it is disturbing that few articles advocating the use of topical or internal tacrolimus in patients with high sensitivity take into account that this topical immune agent may increase the risk of squamous cell carcinoma as well as tumors of the blood system, however, for a new drug that has not yet stood the test of time, its risks need to be considered very carefully, and the drug can be used for the skin or mucous membranes of the skin or mucous membranes that can be widely treated with topical steroids [9]. In earlier studies, we found that the use of immunosuppressant's such as glucocorticoids resulted in an increased risk of squamous cell carcinoma, basal cell carcinoma, and Hodgkin lymphoma, so surveillance biases were unlikely to explain the observed associations. The incidence of skin cancer and non-Hodgkin lymphoma has increased worldwide [10-13]. This suggests that these malignant tumors may have a common cause, perhaps related to the heavy use of immunosuppressant's [14].

We found that previous animal experiments have demonstrated that immune agents in mice can indeed lead to the development of lymphatic system tumors, including cyclosporine and tacrolimus [15]. Prior studies with ciclosporin have shown that topical application of the drug in the DMBA／TPA model inhibited tumour formation in mice, while systemic immune suppression with ciclosporin accelerated carcinogenesis [16,17]. There is evidence that this differential outcome is related tothe differential effects of ciclosporin, i.e. local anti-inflammatory action and systemic immune suppression [18]. The preclinical topical carcinogenicity studies with tacrolimus, which have resulted in a significant lymphoma signal in mice have shown that systemic immune suppression can be achieved with a protocol of daily application of the 0.1% tacrolimus ointment formulation[19].

Sánchez-Pérez J et al demonstrated that nowadays there doesn't exist scientific evidence of an increase of skin cancer, lymphomas or systemic immune suppression in those patients that use or have used topical tacrolimus. Nevertheless, it is not possible to exclude the possibility that there appear cutaneous and/or systemic long-term side effects [21,22].

Conclusion

In this case, our diagnosis suggests that Proliferative lesions (resembling nodular lymphocyte-predominant Hodgkin lymphoma) is indirectly and probably caused by long-term use of the immune drug tacrolimus in pediatric patients with a hypersensitivity system. Early diagnosis can improve the survival of patients, who are prone to relapse, but have a longer survival even if they relapse.

Declarations

Consent to participation and ethical approval: This article is a case report, hence, this research was exempt from the ethical approval statement and the necessity of informed consent.

Data and materials accessibility

The datasets used in this investigation may be found in The First People's Hospital of Xiangtan City.

Competing interests: There are no competing interests declared by the authors.

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Contributions of Authors: Shixuan Peng was in charge of the report's overall execution and manuscript writing, while Yongjun Wu was in charge of collecting the data and diagnosing the disease.

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