

Lymphedema As The Initial Symptom of Lymphoma

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Abstract

Background: To investigate the clinical features of lymphoma with lymphedema as the initial manifestation.

Methods: We performed a retrospective study of 4676 patients with lymphedema treated at the Department of Lymphatic Surgery, Beijing Shijitan Hospital, Capital Medical University, from May 22, 2007, to December 31, 2018. Clinical manifestations and a series of conventional analyses (laboratory tests, ultrasonography, magnetic resonance imaging, computed tomography, and radionuclide imaging) were used to study these cases. Bone marrow aspiration and biopsy tests were used to support the diagnosis of lymphoma. Eleven patients of lymphoma with lymphedema as the first symptom were selected, and their clinicopathological features were analyzed retrospectively.

Results: A total of 11 cases of lymphedema caused or aggravated by lymphoma were found, including 1 case of upper extremity edema, 9 cases of lower extremity edema and 1 case of systemic edema. These patients often accompanied by clinical symptoms such as feeble, emaciation, pain, mass, lymph node enlargement and so on. The proportion of patients with abnormal tumor markers was 66.7% (4/6), the prevalence of anemia among patients with malignant lymphedema was 45.5% (5/11), and the positive rates of ultrasonography, CT and MRI were 100.0% (7/7), 100.0% (8/8) and 100.0% (2/2), respectively. Eleven cases with lymphoma were confirmed by pathological diagnosis. To analyze the clinicopathological features, the main points of diagnosis were summarized.

Conclusions: Lymphoma with lymphedema as the first symptom is extremely rare. It has a hidden onset. To avoid delays in the diagnosis and therapy of lymphoma, physicians should actively look for signs or symptoms of lymphedema during the follow-up period and promptly manage patients developing problems.

Background

The lymphatic system is a part of both the circulatory and immune systems. It has several critical functions in regulating different parts of the homeostasis of the body. As a part of the circulatory system, the lymph system drains surplus fluid from the tissues and returns leaked proteins from the interstitium to the blood. The other important function is to protect the body from infectious and foreign agents.

Lymphedema is defined as the abnormal accumulation of protein-rich interstitial fluid that occurs primarily as a consequence of malformation, dysplasia, or acquired disruption of lymphatic circulation. Lymphedema is distinguished as primary and secondary forms. Primary lymphedema is caused by an inherent defect in the lymphatic vessels or lymph nodes. Secondary lymphedema is the result of various causes, such as trauma, infestation, infection, persistent inflammation, venous disease, extreme chronic immobility, malignancy, surgery, and radiation^(1,2). The lymphedematous limb has a high propensity for bacterial, fungal and viral infections and is also at risk for the onset of malignant tumors and their metastases⁽¹⁾. Due to the typical symptoms of lymphoma are insignificant in some patients,

lymphedema is sometimes the first symptom. The latter is often difficult to differentiate from other systemic diseases, such as limb vascular disease and nephrogenic, cardiogenic and other systemic diseases.

A total of 4676 patients with lymphedema were treated in our hospital from May 22, 2007 to December 31, 2018, including 11 patients with lymphedema caused or aggravated by lymphoma. The aim of this study was to retrospectively analyze the clinical characteristics of these patients and explore the early diagnosis of lymphoma with lymphedema as the initial presenting symptom.

Methods

Research subjects

After obtaining institutional review board approval, we performed a retrospective review of 4676 patients with lymphedema in the Department of Lymphatic Surgery, Beijing Shijitan Hospital, Capital Medical University, between May 22, 2007 and December 31, 2018.

Inspection method

According to the classification of lymphedema (primary and secondary), 4676 patients with lymphedema in our study were subjected to laboratory tests, ultrasonography, magnetic resonance imaging (MRI), computed tomography (CT) or radionuclide imaging. Bone marrow aspiration and biopsy tests were used to support the diagnosis of malignancy. By analyzing the clinicopathological features of 11 patients with lymphedema caused or aggravated by lymphoma, we summarized the main diagnostic points.

Statistical analysis

SPSS ver. 20.0 (SPSS Inc., Chicago, IL, USA) was used for all analyses. A p value less than 0.05 was considered statistically significant.

Results

Clinical Characteristics

We performed a retrospective review of 4676 patients with lymphedema between May 22, 2007, and December 31, 2018. A total of 115 patients with lymphedema caused or aggravated by malignant tumors were found. Furthermore, a total of 11 patients with lymphedema caused or aggravated by lymphoma were found too. Eight patients were men and 3 patients were women. In all, 1 patient had upper extremity lymphedema, 9 patients had lower extremity lymphedema, and 1 patient had systemic edema. The age range of 11 patients with lymphoma was 41 to 79 years (average age: 61.0 ± 12.5 years). The time from the occurrence of lymphedema to the diagnosis of lymphoma ranged from 1 to 24 months (median time: 7.0 months). These patients also accompanied by clinical symptoms such as feeble, emaciation, pain,

mass, lymph node enlargement and so on. The clinical features for each patient are summarized in the Table 1 and Table 2.

Auxiliary examination

The proportion of patients with abnormal tumor markers in this group was 66.7% (4/6), including CA125 (1 case), urinary Ig kappa light chain (3 cases) , serum β 2-microglobulin (1 case), urinary Ig lambda light chain (2 cases), serum Ig kappa light chain (2 cases), and urinary β 2-microglobulin (1 case). The prevalence of anemia among patients with malignant lymphedema was 45.5% (5/11). Some suspicious lesions were investigated with imaging examinations. The positive rates of ultrasonography, CT and MRI were 100.0% (7/7), 100.0% (8/8) and 100.0% (2/2), respectively.

Pathological diagnosis

Eleven cases of lymphedema with malignant tumors were pathologically confirmed to be originated from lymphatic tissue, including 8 cases of mature B-cell lymphoma and 3 case of mature T-cell lymphoma (Table 3).

Discussion

Lymphoma is still one of the most common malignancies in the world. There were 83,087 new Hodgkin lymphoma cases and 23,376 deaths, with 544,352 new non-Hodgkin lymphoma cases and 259,793 deaths in 2020⁽³⁾. The clinical manifestations of lymphoma are diverse, and most cases are diagnosed at an advanced stage due to limitations of current diagnostic techniques. In the diagnosis of lymphoma, lymphedema may be the initial and sometimes the only manifestation in a certain proportion of patients. Hawkins found that of 10 cases of lymphedema from lymphoma, unilateral leg edema was the only presenting symptom in seven cases⁽⁴⁾. Similarly, Smith reported that of 35 cases of lymphedema from neoplasms noted palpable inguinal lymph nodes in all eight lymphoma cases, with three cases having edema as the first manifestation of the disease⁽⁵⁾. In the present study, one patient with lower limb lymphedema was initially mistakenly considered to be related to the treatment of gynecologic malignant tumors. Ten patients with limb lymphedema were initially mistakenly considered to have primary lymphedema. However, further work-up revealed that lymphedema might actually be a manifestation of an underlying lymphoma resulting in lymphatic or venous obstruction.

The previous researches show that there is a certain degree of correlation between lymphedema and lymphoma. The most common neoplasms that are seen in the context of immunodysregulation are lymphomas. Thus, abnormal lymphoid proliferation might be causally related to lymphatic stasis⁽⁶⁾. Inadequate lymphatic drainage may disrupt the regularity of lymphocyte and Langerhans cell trafficking, on which immunocompetence depends, and make the lymphedematous region an immunologically vulnerable area, predisposing patients to infection and oncogenesis. Some theories attempting to explain the mechanism have been put forward. Futrell and Myers highlighted the immunological status governing the response of animal hosts to skin-implanted tumors, with or without an intact lymphatic system. In

their study, although the tumor solution failed to induce malignancy when injected into an area where the lymphatic vessels had been spared, large and lethal tumors developed whenever the injection was in an area where the lymphatics had been impaired⁽⁷⁾. It is also believed that deficiencies in the lymphatic drainage system hamper early recognition of tumor-specific antigens⁽⁸⁾. Chronic stasis produces local changes in the lymphatic protein composition (decreased alpha-2 globulin fraction and increased albumin-globulin ratio) and delaying protein transportation from the interstitial space into the lymphatic tissue might change the tissue antigenic composition and/or regional immunological competence. Lymphatic stasis and remodeling of connective tissue lead to local immunodeficiency. In addition, systemic immunodeficiency or systemic factors such as potential carcinogenic viral infections (human papillomavirus) also explain the etiology of tumors^(1,9).

Malignant lymphedema is an accumulation of interstitial fluid caused by tumor infiltration or compression of the lymphatic vessels or tumor metastasis to lymph nodes that block lymphatic reflux⁽¹⁰⁾. It is commonly encountered in the outpatient setting. When the diagnosis of lymphedema is made, the clinicians must maintain a high clinical awareness of lymphoma as a possible aetiology of lymphedema. The author believes that the following clinical features are helpful for diagnosis:

1. Medical history and physical examination:

1) Age of onset: The age range of 11 patients with lymphoma was 41 to 79 years (average age: 61.0 ±12.5 years), of which 9 cases (81.8%) were over 50 years old. Therefore, lymphomas usually present in elderly patients and arise a long time after the appearance of lymphedema.

2) The duration of edema: Chronic limb edema is commonly due to venous insufficiency and less commonly due to lymphedema, either primary or secondary⁽¹¹⁾. In developed countries, the most common cause of secondary lymphedema is malignancy^(12,13). The time from the occurrence of lymphedema to the diagnosis of lymphoma ranges from 1 to 24 months (median time: 7.0 months), suggesting that close follow-up is necessary for patients with chronic lymphedema for early detection of lesions.

3) The manifestation of edema: lymphedema itself never cause paresthesias or weakness. However cancerous spread, which extrinsically compresses or invades lymphatics, also affect adjacent neurological tissues. Malignant lymphedema often have an acute onset, show rapid progression, result in changes in skin color and be accompanied by pain, paresthesia, paralysis and weakness⁽¹⁴⁾. In addition, severe swelling often occurs in the lower abdomen, perineum and buttocks affected by the tumor.

4) Physical examination: Key components of the physical examination should include the BMI value, distribution of the edema, tenderness of the edema site, presence of pitting edema and varicose veins, any skin changes and any signs of systemic disease including abdominal/pelvic masses or lymphadenopathies⁽¹¹⁾. There are some key-signs that need our special attention. whether there are swollen lymph nodes or masses in the inguinal or axillary region; whether there is cyanosis and venous reflux disorder (congestive changes of the surface veins) or nerve compression (with local pain or

abnormal function of the affected limbs); whether there are changes in the skin appearance (rash, color change, necrosis or ulceration, etc.)⁽¹⁵⁾. In addition, skin metastases often appear as hard, discrete, reddish nodules that can serve as indirect evidence of highly suspicious cases. Despite its rare occurrence, lymphedema may be the initial and sometimes the only finding in those with occult lymphoma, especially for those without B-symptoms and no response to the conventional oedema therapy⁽¹⁶⁾.

5) Past medical history: Key questions in the history should include a complete list of medications and any history of systemic disease, including sleep apnea and malignancy or radiation in the abdominal/pelvic region. A total of 9.1% of patients in this group had a history of malignant tumors. Therefore, when diagnosing lymphedema, special attention should be given to limb swelling caused by tumor recurrence⁽¹⁷⁾.

2. Auxiliary examination: Sixty-seven percent of the patients in this group had abnormal tumor marker results. Nearly half of the patients had varying degrees of anemia. Serum tumor markers and anemia could play a potentially vital role in the surveillance of these difficult cases. Furthermore, a CT scan is the standard procedure for the assessment of disease extension. A pretreatment PET scan is recommended before initiation of therapy; however, PET scans are more widely used to assess the response to therapy. The groin, axillary and suspicious sites were routinely examined by imaging methods with high detection rates, including ultrasound (100.0%), CT (100.0%), and MRI (100.0%). The above examination methods have a very important role in the diagnosis of lymphoma. When the imaging examinations are abnormal, inflammation of the lymphatic drainage area and tissue damage caused by surgery should be excluded in combination with the medical history and other examinations.

3. Pathological diagnosis: Excisional biopsy with histological examination of the lymph nodes is the gold standard for diagnosis. When suspicious tumors or lymph nodes were found by physical examination or the puncture results were negative, surgical resection and pathological examination were necessary to confirm the diagnosis. When it is difficult for surgical resection of tiny tumors, ultrasound-guided biopsy can often obtain satisfactory pathological findings. When accompanied by venous reflux or neurological compression, a mass or lymph node biopsy may be performed. Above all, pathological examination not only confirms the diagnosis but also provides a basis for further treatment.

In Europe and the United States of America, tumors are the most common cause of secondary lymphedema, including lymphedema caused by invasive growth of the tumor and lymphedema caused by tumor treatment (surgical and/or radiotherapy)⁽¹⁷⁾. Some lymphoma may not be detected early due to the concealment of the primary lesion. When lymph node metastasis occurs, lymphedema sometimes becomes the first symptom. In addition, the chronic skin changes seen in patients with prolonged lymphedema are difficult to interpret and may need review by a dermatologist with experience in lymphedema⁽¹⁸⁾. The importance of early diagnosis and early treatment is indicated because lymphoma tends to progress and causes severe physical and psychological problems for

patients owing to chronic swelling, impaired physical function, recurrent infections and disfiguring skin changes^(19,20).

Conclusions

In conclusion, lymphedema caused by lymphoma is a chronic progressive disease with a poor prognosis. To a certain extent, lymphedema may be the initial complaint or even the only finding in some patients. Awareness of this may lead to the earlier diagnosis of an occult neoplasm and earlier anticancer treatments to improve survival.

Declarations

Ethics approval and consent to participate

This manuscript was approved by the institutional ethical review board of Beijing Shijitan Hospital, Capital Medical University.

Consent for publication

As the present study only collected retrospective clinical data and does not pose a risk to the participants, written informed consent was not required.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors declare that they have no competing interests.

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Authors' contributions

KH, JF X, YG S, and WB S collected the data. KH and JF X did the analysis and interpretation of data; KH and WB S conceptualized and wrote the manuscript. Grant to KH financed this study. All the authors approved the version to be published.

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Tables

Due to technical limitations, tables 1,2 and 3 are only available as a download in the Supplemental Files section.

Supplementary Files

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