



## Chronic urticaria associated with malignancies: A review article

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### Review Article

#### Abstract

**BACKGROUND:** Chronic urticaria is a cutaneous disorder defined by the presence of hives and flare for over six weeks. Etiology of chronic urticaria is not clear in 80 to 90 percent of patients. Malignancies are possible associations with allergic disorders such as urticaria. The purpose of this article was to review the expression of chronic urticaria with various malignancies.

**METHODS:** We searched in PubMed, Scopus, and EMBASE databases in English using the keywords chronic urticaria, urticarial, malignancy, and cancer. Inclusion criteria were both full and brief articles, case reports, case series, and original article up to June 2018.

**RESULTS:** We found 258 articles on the primary search. After screening by two researchers, 23 articles were included. Most studies failed to find a link between hives and malignancy. Four studies showed a relationship between hives and malignancy. Five studies showed no relationship between hives and malignancy, and suggested that urticaria could even have a protective effect. As there were no homogenous results, we could not write a meta-analytic study.

**CONCLUSION:** The relationship between chronic urticaria and malignancy is not clear. We need a more organized researches to clarify the association between urticaria and malignancies.

**KEYWORDS:** Urticaria, Neoplasm, Skin, Association

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### Introduction

Chronic urticaria is a cutaneous disorder defined by the presence of hives and flare, on most days of the week, for more than six weeks. Angioedema may be associated with chronic urticaria.<sup>1,2</sup> About 20 percent of the general population could experience urticaria in their lifetime, although the acute form is more common.<sup>3</sup> However, the prevalence of urticaria is varied in different regions of the world.<sup>1</sup> Chronic urticaria is more common in adults than children, and affects about 0.1 to

3 percent of people. Women are affected twice as often as men.<sup>1,2</sup>

The etiology of chronic urticaria is not clear in 80 to 90 percent of patients.<sup>4</sup> Some etiologies of chronic urticaria are thyroid disorders, physical urticaria, parasites, infections, Helicobacter pylori, autoimmune diseases, malignancies, etc.<sup>1</sup> Lesions that last longer than 24 hours and/or are painful or burn or residual bruises suggest vasculitis. Chronic urticaria has pruritus that is exaggerated at night. Trigger factors of chronic urticaria are physical factors, drugs, stress, and food. Patients with allergy such as patients with chronic urticaria are more sensitive to psychopathological features including

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loneliness, tension, confusion, stress, agitation, obsession, and depression, and their quality of life is not well.<sup>5</sup>

Spontaneous resolution occurs in most patients with urticaria; the mean duration of the disorder is two to seven years. Urticaria is usually diagnosed using patient history and physical examination. Malignancies are a possible association with allergic disorders such as urticaria, although data on this matter are not unequivocal.<sup>6</sup> Clinical manifestations such as fever, weight loss, arthralgia, arthritis, cold or heat sensitivity, abdominal pain, and bone pain needs further investigation for systemic disorders such as malignancies. Moreover, significant increase of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) suggests a serious etiology including malignancies. Therefore, malignancy screening is suggested in specific patients. Avoiding triggers is baseline therapy in chronic urticaria, if any trigger is identified.<sup>7</sup> This study aimed to make a review on the association of chronic urticaria with malignancies.

### Materials and Methods

There is controversy about the relationship between allergy and malignant diseases. It is therefore necessary to write a meta-analytic review article; but as we did not find homogeneous articles in the initial search, we decided to write a systematic review article instead.

The data were searched in PubMed, Scopus, and EMBASE databases in English. Our search keywords included chronic urticaria, urticaria, malignancy, and cancer. Inclusion criteria were full and brief articles, all ages, genders, case reports, case series, and original articles. Exclusion criteria were abstract article, and articles that did not investigate urticaria and malignancy together. We did not have time limits to start our search and we continued up to June 2018.

Initially, two researchers searched

individually, then we selected articles that looked at the relationship or association between urticaria and malignancy.

### Results

After evaluation of all data, we found 258 articles on the primary search. After screening by two researchers, 23 articles were entered the study including 8 original articles, 1 case series, 1 review article, and 13 case reports (Table 1). Most of these studies were done in the United States (10 out of 23). Most studies failed to find a link between hives and malignancy. Four studies had shown a relationship between hives and malignancy, and five studies declared no relationship between hives and malignancy, and suggested that urticaria could even have a protective effect. The type of malignancy was different in the most of the studies, but carcinoma and hematologic malignancies were more common in patients with urticaria.

### Discussion

The relation between chronic urticaria and malignancy has not yet been clarified. Few epidemiologic studies are available about this association. Four articles showed the association between chronic urticaria and malignancy.<sup>8-11</sup> Most of the found studies were case reports with low evidence-based medicine value. Between the epidemiological studies, Chen *et al.*<sup>8</sup> study is one the largest studies with 12720 patients with chronic urticaria treated with antihistamines for the duration of 6 months to 2 years. They showed that chronic urticaria was associated with increased risk of malignancy, especially hematologic malignancies (35 cases of non-Hodgkin lymphoma and 22 cases of leukemia). They stated that diagnosis of urticaria in the first year of the disease is a risk factor for malignancy.<sup>8</sup> In 1988, McWhorter<sup>9</sup> found that patients with history of allergy were associated with increased subsequent malignancies, especially in those with hives.

**Table 1. The distribution of different finding in patients with cancers and chronic urticaria**

Author	Cancer kind	Cancer frequency	Country	Patients count	Association
Chen et al. <sup>8</sup>	Different	704	Taiwan	12720	+
McWhorter <sup>9</sup>	Different	341	United States	6913	+
Karakelides et al. <sup>10</sup>	Different	166	United States	1639	+
Greiner et al. <sup>11</sup>	Lung small cell carcinoma	1	Germany	1	+
Wang and Diepgen <sup>12</sup>	Different		Germany	Cancers & chronic urticaria	Reverse
Vena et al. <sup>13</sup>	Different		United States	13665	Reverse
Linabery et al. <sup>14</sup>	Review		United States	Leukemia	Reverse
Severson et al. <sup>15</sup>	AML		United States	98	Reverse
Wen et al. <sup>16</sup>	ALL children	1842	United States	1842	Reverse
De et al. <sup>17</sup>	Lung large cell carcinoma	1	United Kingdom	1	+/-
Lindelof et al. <sup>18</sup>	Different	36	Sweden	1155	-
Krishnan and Ownby <sup>19</sup>	Mastocytoma	1	United States	1	+/-
Eriksson et al. <sup>20</sup>	Different	119	Sweden	6224	+/-
Eriksson et al. <sup>21</sup>	Different	2	Sweden	6593	+/-
Merrill et al. <sup>22</sup>	Different		United States	Atopic patients	+/-
Campanelli et al. <sup>23</sup>	Colon adenocarcinoma	1	Switzerland	1	+/-
Manganoni et al. <sup>24</sup>	Thyroid carcinoma	4	Italy	4	+/-
Baroni et al. <sup>25</sup>	Prostate carcinoma	1	Italy	1	+/-
Hu et al. <sup>26</sup>	Lung adenocarcinoma	1	China	1	+/-
Murota et al. <sup>27</sup>	B cell	1	Japan	1	+/-
Shamsadini et al. <sup>28</sup>	Cerebellar astrocytoma	1	Iran	1	+/-
Zhang et al. <sup>29</sup>	IgA Myeloma	1	Japan	1	+/-
Clore et al. <sup>30</sup>	Hairy cell leukemia	1	United States	1	+/-

ALL: Acute lymphoblastic leukemia; AML: Acute myelogenous leukemia

+: Chronic urticaria associated with cancer

Reverse: Chronic urticaria prevent the cancer

+/-: Not protection, not association

Five studies showed that chronic urticaria could be protective against cancer.<sup>12-16</sup> Of course, one of them is a review article.<sup>14</sup> They showed inverse relationship between atopy and leukemia Acute lymphoblastic leukemia (ALL). In 2005, Wang and Diepgen showed that atopic disorders are associated with a reduced risk for malignancies (pancreatic cancer, childhood leukemia and brain tumors).<sup>12</sup> Allergies, especially related to atopy, due to hyperactive immune system may be associated with a lower risk of pancreatic malignancy.

A few studies showed no relation between chronic urticaria and malignancy such as Lindelof et al. study.<sup>18</sup> These articles supported that allergic disorders (type I allergy) such as

asthma, allergic rhinitis (AR), eczema, and urticarial were not related to the individual's risk of cancer.<sup>18,20</sup>

Most articles (n = 20) showed controversial results between chronic urticaria and malignancy. They declared that atopy did not have protective effect against cancer, nor induced cancer;<sup>21,22</sup> however, association or relation between atopic disorders and malignancy is controversial.

The type of malignancy was different in the most of studies. Carcinoma and hematologic malignancies such as leukemia were most common, and lymphoma was less common.

Between case reports, lung carcinomas were the most common; De et al.<sup>17</sup> suggested

a plain chest X-ray be taken in a patient with chronic urticaria, although the pulmonary tumor is uncommon with hives. Lung carcinomas were only observed in adult patients with chronic urticaria. Mastocytosis may be associated with chronic urticaria, which we should consider in the differential diagnosis of chronic urticaria.<sup>19</sup>

In 80 to 90 percent of patients with chronic urticaria, there is no identified etiology. Most researchers suggested complete blood count (CBC) with differential, CRP or ESR, liver function tests (LFT), and thyroid-stimulating hormone (TSH) level; although these tests are normal in most cases without systemic disease manifestations. Skin biopsy is needed for the diagnosis of urticarial vasculitis, and patients suspected of mastocytosis.<sup>14</sup>

Reviewing existing articles, lymphatic-hematopoietic cancers (leukemia, lymphoma, and myeloma) were the most common. There were a few articles that showed lymph-reticular diseases and related malignancies (more common), and carcinoma (less common) are increasingly associated with chronic urticarial.<sup>12</sup> An article reported internal diseases were prevalent in 1.6% of patients with chronic urticaria.<sup>23</sup> O'Donnell and Havyer reported a case of breast cancer in a woman with chronic urticaria. They concluded that patients with resistant chronic urticaria without a known cause should be screened for malignancies.<sup>31</sup> In a recent study, the risk of cancer was potentially raised in patients with chronic urticaria. The study suggests that at least a mammography/prostate antigen test assessment, and in cases of chronic urticaria, an ultrasonography of the thyroid gland is recommended.<sup>32</sup>

### Conclusion

Because there were no homogenous articles in our search, the relationship between chronic urticaria and malignancy is not clear. We need more organized researches for clarifying the association between chronic urticaria

and malignancies.

### Conflict of Interests

Authors have no conflict of interests.

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