

## REVIEW

# Viral infection in thymoma and thymic tumors with autoimmune diseases

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**Abstract**

A thymoma is a type of thymic tumor which is rarely malignant that is frequently reported in adult patients. A number of thymoma-related immune disorders are observed including autoimmune diseases, which suggests a strong connection between thymoma development and immunological mechanisms. Characterized by association with humoral and cellular immunodeficiency, thymoma patients are susceptible to opportunistic infections by environmental factors. Recent reports have suggested that viral infection may play a role in the etiological mechanisms of thymoma development associated with dysregulated immunity. In this review, we summarize the case reports and studies related to viral infection, such as CMV, EBV and HSV, that probably play a part in the pathogenesis of thymoma and related diseases. Furthermore, we demonstrate the underlying mechanisms by which viruses may induce the occurrence of thymoma with autoimmune diseases. Lastly, we discuss the potential application of antiviral therapy in the treatment of thymic diseases.

**KEYWORDS**

autoimmune diseases, infection, thymoma, virus

**INTRODUCTION**

As one of the less malignant neoplasms of thymic epithelial cells (TECs), thymoma is characterized as a benign tumor that grows slowly and rarely metastasizes. The relationship between thymoma and a series of autoimmune diseases (AIDs) has been demonstrated by several research groups. It has been estimated that nearly 50% of thymoma patients develop myasthenia gravis (MG), while thymomas are discovered in almost 80% of MG patients.<sup>1</sup> Moreover, thymoma is relevant to immunodeficiency in some adult patients that develop hypogammaglobulinemia, namely Good's syndrome (GS). B and T cell immunodeficiency are found in patients with GS and only 6% to 11% cases of thymoma are connected to this syndrome.<sup>2</sup> According to the World Health Organization, there are several subtypes of thymoma classified as A, AB, B1, B2 and B3, or mixed type, by their characteristic of epithelial cells and

lymphocyte content. In addition, four clinical stages of thymoma are determined by the Masaoka staging system, which is a valuable prognostic factor for determining whether to perform a thymectomy in different thymoma patients. Although thymoma is uncommon with a low incidence of malignancy, the interrelationship between thymoma and immune disorders suggests that some other factors may be involved in the pathogenesis of thymic-related diseases.

Recently, it has been suggested that excluding genetic background, environmental factors or infectious agents also appear to play a part in the occurrence of thymoma or thymic diseases. A variety of virus-associated cases have been observed by several research groups worldwide. More importantly, the onset of thymoma and immune dysfunction simultaneously in one patient implies the involvement of pathogens such as bacteria and virus, which could infect the human thymic epithelium.<sup>3,4</sup> A wide spectrum of viruses

has been detected following pathological examination of the human thymus, including herpes viruses and retroviruses.

In this review, we focus on recent investigations related to viral infection in thymoma or thymic-associated diseases. These include case reports and studies of virus-involved pathology of thymoma and related diseases. Human herpesviruses such as CMV, EBV and other viruses in pathogenesis of thymoma and related diseases are summarized. We further discuss the role of these viruses in the etiological mechanism of autoimmune diseases accompanying thymoma or thymic disorders. In the final part of this review, we highlight the future benefit of antiviral therapy in the treatment of thymic tumors and associated autoimmune diseases.

## VIRAL INFECTION IN THE PATHOGENESIS OF THYMOMA AND RELATED DISEASES

The association between many malignant tumors and viruses is well documented, while tumors of low malignancy such as thymoma are as yet to be fully investigated. During the past two decades, herpesviruses such as CMV, EBV and HSV have been the most characterized viruses in studies on the thymus (Table 1). There are reports of virus-positive cells being found

in thymomas or the thymus of MG patients that implicate there is a possible relationship between this pathogen and thoracic diseases. Furthermore, an increasing number of studies have indicated the presence of virus particles or viral genes in human thymocytes, thymomas or other thymic-related neoplasm.

## CMV infection in thymoma and related diseases

Cytomegalovirus (CMV) belongs to the *Betaherpesvirinae* subfamily, and has a well established tropism for the human salivary glands as well as being found in other nonhuman-primates. In several studies, more than 40% of adults were found to be positive for CMV infection, and most patients were immunocompromised. There was little evidence of an association between CMV infection and malignant tumors;<sup>32,33</sup> however, CMV has been discovered in several thymoma patients in recent studies.<sup>10,34,35</sup>

## CMV retinitis with thymoma

Several case reports have previously described thymoma patients with CMV infection and hypogammaglobulinemia,

**TABLE 1** Viral infections in thymoma and related diseases

Virus	Related diseases	Detection methods	References
CMV	Thymoma/GS/retinitis	PCR	5–9
	Thymoma/GS/encephalitis	PCR	10,11
	Thymoma/GS/enterocolitis	PCR	7
	Thymoma/GS/duodenoenteritis	IFS	12
	Thymoma/GS/PRCA	IHC	7,13
EBV	Thymoma/MG	PCR	14
	Thymoma	Southern blot/PCR/ISH	15
	Lymphoepithelioma-like thymic carcinoma	Southern blot/PCR/ISH	16
	Lymphoepithelioma-like thymic carcinoma	ISH	17,18
HSV-1/2	Lymphoepithelioma-like thymic carcinoma	ELISA/IHC	19
	Thymoma/oral herpetic infection	ELISA	20
	Thymoma/GS/pulmonary and urinary tract infection	ELISA	21
	Thymoma/GS	PCR/IHC	22
	Thymoma/GS/oral candidiasis	Virus culture	23
HTLV	Thymoma/GS/meningitis	PCR	24
	Thymoma/MG/thymic hyperplasia	PCR/ELISA/WB	25
KSHV	Thymoma/erythroblastopenia	PCR	26
Poliovirus	Thymoma/thymitis	PCR/IHC/IFS	27
Retrovirus	Thymoma	EM/RT activity assay	28
WNV	Thymoma/MG	ELISA	29
HPyV7	Thymoma/MG	PCR/IHC/ISH	30
HB19V	Thymoma/thymic hyperplasia	PCR/IHC	31

Abbreviations: CMV, cytomegalovirus; EBV, Epstein–Barr virus; ELISA, enzyme-linked immunosorbent assay; EM, electron microscopy; GS, Good's syndrome; HB19V, human parvovirus B19; HPyV7, human polyomavirus 7; HSV-1/2, herpes simplex virus-1/2; HTLV, human T lymphotropic virus; IFS, immunofluorescence; IHC, immunohistochemistry; ISH, in situ hybridization; KSHV, Kaposi's sarcoma associated herpesvirus; MG, myasthenia gravis; PCR, polymerase chain reaction; PRCA, pure red cell aplasia; RT, reverse transcriptase; WB, western blot; WNV, West Nile virus.

a systemic disorder. The association between thymoma and hypogammaglobulinemia was first reported by Good and is now known as Good's syndrome. Good's syndrome patients usually develop opportunistic infections, including CMV infection and pulmonary diseases caused by other pathogens. Sen et al. report a case of malignant thymoma in a patient diagnosed with Good's syndrome. The patient had a history of a decline in vision and aqueous humor polymerase chain reaction (PCR) test indicated high numbers of CMV, suggestive of CMV retinitis. Interestingly, the viral load of CMV decreased to 0 copy/ml in 2 weeks after antiviral therapy. No recurrence of CMV retinitis was observed 7 months later. Therefore, this case demonstrates the potential role of CMV in immunodeficient patients with thymoma.<sup>5</sup> There are further studies concerning patients with thymoma excision, visual loss and Good's syndrome. The aqueous humor or vitreous fluid samples from two patients with thymoma were found to be positive for CMV DNA by PCR analysis, which is clinically consistent with CMV retinitis.<sup>6,7</sup> Similarly, the visual acuity of one case was enhanced and CMV retinitis was controlled after 1 month of intravenous antiviral therapy.<sup>6</sup> According to Huissoon et al., a patient was found to be CMV positive following PCR analysis of a vitreous fluid biopsy and CMV antigen detection from blood. Thymoma was then diagnosed by chest X-ray during subsequent therapy. Although CMV antigen may have led to the dysregulation of the T cell level, the patient had a normal CD4/CD8 ratio, which is not a common finding in thymoma. In view of the inhibition of CMV latency could not be observed, and the authors of this study proposed that a relationship existed between thymoma and the incapacity of CMV-specific immunity.<sup>8</sup> A 50-year-old man was found to be suffering from panuveitis in the right eye, which was further confirmed positive for CMV by PCR analysis of a vitreous fluid sample. He had a type B2 thymoma which was finally diagnosed as CMV retinitis with Good's syndrome. This patient is therefore the first case where thymoma and hypogammaglobulinemia were initially demonstrated by CMV retinitis.<sup>9</sup> The clinical features of these cases suggest that there is probably an association between CMV infection and the onset of autoimmune retinopathy.

### CMV encephalitis with thymoma

In the report by Cucchiara and colleagues, a spindle cell thymoma case that was resected and tested for CMV using PCR cerebrospinal fluid (CSF) examination is described. The patient had a progressive cognitive decline and was subsequently diagnosed with CMV encephalitis with Good's syndrome.<sup>10</sup> In another report, following resection of an epithelial thymoma, another elderly male patient was verified as CMV positive by quantitative PCR of serum and CSF sample. Good's syndrome associated with CMV encephalitis was diagnosed as his cognition was not intact. Based on the pathogenesis of CMV-related encephalitis in thymoma

patients, the authors supposed early consideration of the possibility of CMV infection should be given in the diagnosis of thymoma patients with Good's syndrome and nervous system disorder.<sup>11</sup>

### Other CMV-associated thymoma diseases

An observation made by Moysse et al. revealed a case of medullary thymoma with an imbalance of CD4/CD8 T lymphocytes. The patient had abundant CMV inclusions in endothelial cells and Kaposi's sarcoma spindle. Additionally, IgG antibody detection was positive for CMV and EBV infection, which suggested an association between these opportunistic infection factors and thymoma.<sup>36</sup> By identification of thymoma and hypogammaglobulinemia, a Japanese group reported an elderly woman who presented with CMV duodenitis. The intracellular inclusion bodies of CMV were discovered by duodenal mucosal biopsy and immunofluorescent staining, which suggested CMV infection. Her abdominal symptoms improved and CMV inclusion bodies had disappeared following CMV-Ig and ganciclovir treatment.<sup>12</sup> Another Group from Japan described a type AB thymoma patient with hypogammaglobulinemia and pure red cell aplasia (PRCA). Intranuclear inclusion bodies were discovered in the tumor which were immunohistochemically positive for CMV. Notably, this is the first thymoma case involving CMV infection of tumor cells, while CD34 were negative and pancytokeratin were positive.<sup>13</sup>

### EBV infection in thymoma and related diseases

Epstein-Barr virus is a member of the *Gammaherpesvirinae* subfamily, which ubiquitously infects the majority of the human population, particularly young people, with the ability to establish lifelong latency. Whilst EBV infection is usually latent and benign, malignant transformation or autoimmunity disorder may occur in some cases. In addition, EBV is well known for its association with a wide variety of malignant tumors, including Burkitt's lymphoma, Hodgkin's lymphoma, X-linked lymphoproliferative syndrome, nasopharyngeal, gastric and thymic carcinomas.

### EBV infection in patients with thymoma

The association between EBV and thymoma was first studied by Southern blotting to detect the EBV genome in the 1980s.<sup>37,38</sup> Teoh et al. examined the EBV genome in 13 myasthenia gravis patients with thymoma. The results showed that two patients were positive for EBV, while no EBV was identified in MG patients without thymoma.<sup>14</sup> Another group from Japan investigated the distribution of EBV-infected cells from 11 normal thymuses and 11 thymomas without MG by in situ hybridization (ISH)

using EBV-1 as a probe. EBV was implicated in a few lymphocytes from one thymoma and two normal thymus samples.<sup>15</sup> The presence of EBV-associated thymic tumor indicated a potential contribution of EBV to the development of thymoma in these patients.

### EBV infection in patients with lymphoepithelioma-like thymic carcinoma

EBV DNA has also been evaluated in cases of invasive thymoma and thymic carcinoma.<sup>16,17</sup> By PCR and ISH analysis, two Japanese adolescents were identified as EBV-positive, both of whom were diagnosed with lymphoepithelioma-like thymic carcinoma. Furthermore, the DNA hybridization analysis of one case, with a high antibody titer against EBV, suggested the presence of EBV *Bam*HI-W and *Xho* I fragment in tumor tissues. These results demonstrated that the EBV genome may integrate in the tumor cells.<sup>16</sup> In the report by Sekihara et al., a young male with thymic lymphoepithelioma-like carcinoma was found positive for EBV infection by ELISA and immunohistochemical (IHC) staining. He was treated with chemotherapy but had a poor prognosis.<sup>19</sup> In addition, an observation on 21 thymomas and 20 thymic carcinomas tissues made by Wu and Kuo discovered a tumor resected from a 19-year-old Chinese patient was EBV-positive. The young male's histological type was also lymphoepithelioma-like carcinoma.<sup>18</sup> From these results, it could be speculated that EBV may play a part in the oncogenesis of lymphoepithelioma-like thymic carcinoma.

### Involvement of EBV infection in the pathogenesis of thymic tumors

As previously described, most studies on EBV infection are case reports and concern the detection of viral genes/protein level in thymomas and thymic tumors. The molecular mechanisms of EBV-induced pathogenesis in thymic and autoimmune disorders are poorly understood. By using a double color immunofluorescence approach, functional EBV receptors were identified in a subpopulation of immature human thymocytes. It was found that EBV could establish a stable infection in thymocytes after 6 weeks coculture with virus. In addition, the authors of this study detected EBNA-1 in thymocytes which is significant for EBV episome maintenance. EBV infection of thymocytes may therefore act simultaneously with IL-2 and lead to lymphokine-dependent cellular proliferation.<sup>39</sup> A recent meta-analysis by Zhang et al. systematically reviewed published studies on the role of EBV in the pathogenesis of thymic epithelial tumors (TETs). They found that in comparison with nasopharyngeal carcinoma (NPC) there was a low prevalence of EBV in benign TETs, with or without MG, implying a possibility that EBV may not be an important environmental factor in TET development. In contrast, nearly half of the reported

lymphoepithelioma-like carcinoma (LELC) cases were EBV-positive. EBV may therefore play an essential part in the etiology of LELC.<sup>40</sup> To confirm the potential role of EBV in the pathogenesis of thymoma and thymic tumor, further investigations using more clinical cases and research on virus-host interaction are therefore necessary.

### HSV-1/2 infection in thymoma and related diseases

Herpes simplex virus is a unique virus of high complexity consisting of an envelope and icosahedral capsid. It belongs to the family of *Herpesviridae* and infects a large proportion of the human population worldwide. There are two strains of herpes virus; HSV-1 and HSV-2. Infection with HSV-1 usually lead to blisters on the lip or eye, while genital herpes is always caused by HSV-2 infection. A range of diverse diseases are implicated to be associated with HSV-1 or HSV-2, including encephalitis and meningitis. Over the last few years, there have been several reports which have revealed a correlation between HSV-1/2 infection and immunodeficient diseases accompanied by thymoma.

#### HSV-1 infection in thymoma and related diseases

Aydintug et al. reported a case of a 65-year-old man with immunodeficiency and type AB thymoma. The patient later developed recurrent oral herpetic infections. Results of laboratory examinations showed a high HSV-1 IgG titer, indicating HSV-1 infection. The lesions in this patient completely or partially resolved following systemic antiviral therapy. Patients with thymoma and immunodeficiency are more susceptible to opportunistic viral infection, thus the early diagnosis of HSV-1 infection is critical for a favorable prognosis.<sup>20</sup> A Caucasian female reported as suffering from recurrent pulmonary and urinary tract infections, was found to have a thymoma following chest computed tomography (CT). Serology was positive for HSV-1. There was a reduction in IgG, IgM, CD4+ T and B cell counts, thus Good's syndrome was diagnosed.<sup>21</sup> A further report by Mean et al. described a patient with thymoma who underwent treatment with thymectomy and radiotherapy. The patient was found to have severe hypogammaglobulinemia and both HSV-1 and HSV-2 DNA appeared positive using the PCR method. Viral infection was further confirmed by immunohistochemical staining of liver and lung tissue. In light of previous reports that two immunodeficient thymoma patients died from HSV infection, the authors suggest that more attention is given to the severity of infection by HSV in these patients.<sup>22</sup>

#### HSV-2 infection in thymoma and related diseases

Sicherer and colleagues reported a case of thymoma accompanied by chronic oral candidiasis. The patient was found to

be HSV-2 positive from laboratory data and a thoracotomy was performed. The patient subsequently developed recurrent pneumonia and myasthenia gravis, but no evidence of malignancy was observed. This is the first case of thymoma with cellular immunodeficiency reported at that time.<sup>23</sup> Recently, the first case of Good's syndrome associated with HSV-2 meningitis was reported by Matta et al. The thymoma patient (type A) was positive for HSV-2 on PCR analysis and diagnosed with meningitis because of this viral infection. The findings of inverted CD4/CD8 ratio and severe hypogammaglobulinemia suggested Good's syndrome with thymoma. These data demonstrate a potential interaction between primary immunodeficiency and opportunistic HSV-2 infection of the central nervous system.<sup>24</sup>

### HTLV-I/II infection in thymoma and related diseases

Human T lymphotropic virus type-I (HTLV-I) is an etiological agent of adult T cell leukemia (ATL). HTLV-I can infect human immature thymocytes and contribute to ATL development. A previous study indicated a connection between HTLV pX gene and tumorigenicity in the thymus.<sup>41</sup> Interestingly, HTLV-I infection has been identified in a series of autoimmune diseases, such as arthropathy, polymyositis, Sjögren's syndrome<sup>42-44</sup> and myasthenia gravis.<sup>45</sup>

In their study, Manca et al. reported the amplification of *tax* and *pol* genes of HTLV-I/II in 12 thymoma and 15 thymic hyperplasia patients with MG. The results of PCR demonstrated that positive samples of *tax* and *pol* were found in 92.5% and 55% of patients, respectively. There was a higher positive rate in thymoma patients (91.6% for *tax* in HTLV-I/II and 75% for both genes in HTLV-I). These results were further confirmed by ELISA and western blot assays. In consideration of the relationship between HTLV-I and autoimmune diseases, it could be assumed that this virus contributed to the etiology of MG patients with thymoma.<sup>25</sup> A transgenic rat model carrying HTLV-I pX, the viral gene coding *tax*, was constructed by Kikuchi et al. This model was used to determine which rats developed thymoma and how that occurrence related to pX expression level. The authors detected high levels of pX mRNA in thymomas compared with controls, suggesting a possible role of HTLV-I pX in the development of thymomas.<sup>41</sup> These findings were further implicated by the results in another study where epithelial thymoma developed in the thymus of transgenic rats expressing pX, thereby providing possible evidence for HTLV-involvement in thymomas.<sup>46</sup>

### Other viral infections in thymoma and related diseases

Apart from herpesviruses, a number of investigations have focused on the relationship of other viral infections and thymoma. A 69-year-old woman with thymoma and

erythroblastopenia underwent thymic resection and developed Kaposi's sarcoma lesions. PCR amplification detected HHV-8 DNA in KS samples from the tongue and skin, suggestive of a potential association of KSHV in the onset of KS lesions in thymoma.<sup>26</sup> In their research for evidence of viral infection in thymuses, Cavalcante et al. discovered that two thymomas and two thymitis from 27 thymuses were positive for poliovirus RNA and capsid protein VP1. Subsequently, persistent thymic infection of this positive-stranded RNA enterovirus was also observed.<sup>27</sup> According to Ono et al., retrovirus-like particles were detected in cultured thymus cells of all thymoma tissues using electron microscopy and reverse transcriptase activity assay. Thus, the putative lytic infection of retroviruses may have engaged in the occurrence of thymic disorder like thymoma in humans.<sup>28</sup> Furthermore, there have been studies demonstrating the presence of West Nile virus (WNV), human polyomavirus 7 (HPyV7) and human parvovirus B19 (B19V) in thymoma or thymic hyperplasia.<sup>29-31</sup> The association of viruses with thymic epithelial tumors by these findings raises the possibility of the involvement of viruses in the development of thymoma.

### ASSOCIATION OF EBV INFECTION WITH AIDS ACCOMPANY BY THYMIC TUMORS

Although the relationship between thymic tumors and autoimmune diseases has been demonstrated by several groups, the etiology of AIDs is poorly understood. Notably, numerous studies have suggested a connection between viruses and AIDs, such as MG, systemic lupus erythematosus and rheumatoid arthritis. These findings raise the possibility that viral infection may have participated in the development of autoimmune diseases accompanied by thymic diseases such as thymoma. Therefore, patients with thymoma may develop autoimmune diseases through a virus-involved mechanism. As EBV is the most studied virus in AIDs, increasing evidence support its contribution to the development of AIDs with thymoma or other thymic diseases.

### EBV infection in myasthenia gravis with thymoma

In the last few years, there have been investigations which have focused on the relationship between thymic tumors and MG. A series of studies has demonstrated that EBV infection is related to the pathogenesis of MG with thymic tumors, such as thymoma.

To verify the link between EBV and thymus pathology in MG, Cavalcante et al. analyzed the EBV gene and viral proteins in the thymuses of MG patients. The results showed EBV infection in specimens from all MG patients, and a high proportion of EBV-infected B cells, and several EBV latent and lytic genes and viral proteins were also detected. The authors inferred a mechanism that EBV may reactivate in the host, thus leading to the production of autoantibodies

by EBV-infected B cells and the induction of MG by unknown factors.<sup>47</sup> To profile the genes involved in immune response and inflammation of MG patients, they applied low-density array (LDA) and real-time PCR to investigate the dysregulated gene in MG patients. There were 21 upregulated genes identified, most of which were cytokine, chemokine, growth factor and CD antigen. Intriguingly, the increased expression of several genes suggest the possibility of an immune response against viral infection. The subsequent identification of EBV latent transcripts (EBER-1, EBNA-1, and LMP-1) and lytic transcript (BZLF-1) using quantitative PCR revealed latent and productive infection of EBV in MG thymuses. These findings assumed the hypothesis that EBV infection might take part in the autoimmune response, promote chronic intrathymic inflammation and autoantigen sensitization in MG thymus.<sup>48</sup> In the following study by the same group, they found that the EBV viral load was higher in MG thymomas compare to non-MG thymomas. The highest EBER-1 expression and EBV DNA load was detected in B2 and B2B3-type thymomas. Based on the finding that MG did not develop in all cases, it is worth exploring whether EBV is able to prime autoimmunity in thymoma patients. In addition, EBER-1 was positively correlated with TLR3 expression in EBV-infected MG thymomas, demonstrating the involvement of EBER-1 in regulating the TLR3 pathway in MG patients associated with thymoma.<sup>49</sup> A positive correlation between early-onset MG and high titer of anti-EBNA-1 IgG in serum was observed in MG patients by Csuka et al. Thymoma was found in 46% of patients with early-onset MG. Although there was no association between the titers of anti-AchR and EBNA-1 antibodies, the increased level of EBNA-1 IgG is notable for the diagnosis of autoimmune disorders such as MG.<sup>50</sup>

### EBV infection in other autoimmune diseases

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that usually leads to joint damage. An investigation was conducted in patients with RA to determine whether EBV infection is involved in the pathogenesis of RA. The study revealed that antibodies against EBNA-1, EBV DNA and EBV reactivation in RA patients were higher than those of controls.<sup>51</sup> The EBV DNA load in the PBMCs from RA patients was analyzed using real-time PCR by Balandraud et al. who discovered a 10-fold increase in virus titer in comparison with normal samples.<sup>52</sup> EBV has also been associated with RA by structure analysis demonstrating an interaction between MHC II and the EBV viral glycoprotein 42, which facilitate B cell entry and induce occurrence of RA.<sup>53</sup> In their report, Xiong et al. describe a patient with rheumatoid arthritis accompanied by thymoma and Hashimoto's thyroiditis. However, no examination of viral infection was performed in this study.<sup>54</sup>

Systemic lupus erythematosus (SLE) is considered a chronic inflammatory autoimmune disease that affects a

wide range of organ systems. The association of SLE with thymoma is rare, but there have been studies which have found an association between SLE and EBV.<sup>55,56</sup> The upregulation of EBV early antigen protein D (EA), envelope membrane antigen (MA), LMP-1 and LMP-2A have been observed in PBMCs from SLE patients.<sup>57,58</sup> Interestingly, another study showed EA, MA, LMP-1 and LMP-2A B-cell epitope peptides (EPs) increased SLE-related autoantibodies in mice.<sup>59</sup> A case of an elderly male patient has been described by Haas et al. The patient developed SLE after resection of thymoma with pure red cell aplasia. Although autoimmune diseases such as SLE occur without thymoma, a poor prognosis has been observed in SLE patients accompanied by thymoma.<sup>60</sup> In addition, 14 patients were identified as SLE with thymoma in a 15 year observational study, indicating the coexistence of this autoimmune disease and thymoma.<sup>61</sup>

Sjögren's syndrome (SS) is an organ-specific disorder characterized by lymphocytic infiltration of the salivary and lacrimal glands. Several studies have revealed that EBV DNA and antibodies against EBV were detected in the saliva and serum of patients with SS suggesting the participation of viral infection in SS etiology.<sup>62-64</sup> According to the analysis of Pasoto et al., a higher frequency of EBV early antigen diffuse (anti-EA-D), related to viral replication, was observed in patients with primary Sjögren's syndrome (pSS). The findings of this study implicate a putative role of reactivated EBV in regulating pSS articular involvement.<sup>65</sup> Furthermore, it has been discovered that EBV could be activated by SS saliva, which may contain factors that trigger virus replication. A possible association has been reported to exist between active EBV infection and ectopic lymphoid structures in the salivary glands of SS patients.<sup>66,67</sup> A case of an elderly male patient with thymoma and SS with MG was reported several years ago, and the patient was reported to be in remission after thymic resection.<sup>68</sup>

In summary, the results from recent reports suggest the involvement of EBV infection in the pathogenesis of myasthenia gravis. Although a major role of EBV in MG development could not be confirmed from these data, there is a connection between EBV infection and MS with thymoma. By contrast, there are fewer cases concerning the association of EBV with autoimmune disease other than MG. RA, SLE and SS have been described to be related to either viral infection, or with thymoma and thymic tumors. The number of cases is insufficient to conclude that there is a correlation between virus and these AIDs with thymoma. Thus, further cases and sophisticated studies are necessary to elucidate the underlying mechanism of this association.

### ANTIVIRAL THERAPY IN THYMOMA AND RELATED DISEASES

Previous studies have shown that thymoma patients and severe cellular immunodeficiency are associated with more severe cellular immunodeficiency and a higher risk of viral

infection than those without thymoma.<sup>20</sup> It has also been proposed that viruses play a role in the pathogenesis of thymoma and related diseases in susceptible individuals. We cannot exclude the participation of viruses in the development of immunodeficient or immunocompromised patients associated with thymic tumors. For this reason, the application of antiviral therapy should be considered for the treatment of patients with thymoma and immunodeficient diseases such as hypogammaglobulinemia.

It is worth knowing that a majority of the viruses associated with thymoma are involved in regulating the immune system, and might therefore play a vital role in determining the immunological modification in thymoma patients, such as regulation of Treg or Breg. Viral infections may be critical for the occurrence of some types of thymic disorders and autoimmune diseases, which could recover by clearance of viruses.<sup>5,6,12</sup> Apart from the conventional resection of virus-infected tissue from thymic tumors, it is possible to inhibit viral infection using antiviral agents to reinforce the distinct immune responses against infection. In addition, a vaccine for a virus (e.g., EBV) might also be useful in suppressing, or even preventing, autoimmune diseases in patients with related thymic diseases. The variables of cytokines and other cellular factors due to viral infection might prove to be available as diagnostic markers for monitoring autoimmune response.<sup>48</sup> Moreover, the different immunological and clinical profiles of MG thymoma and non-MG thymoma patients should be taken into account in antiviral treatment.<sup>49</sup> The etiology of autoimmune diseases with thymoma in humans will further be confirmed by establishing *in vivo* models of thymic tumors carrying viral genes. These animal models will be valuable, not only in the research of viral infections that may lead to the elucidation of virus-related thymic abnormalities, but also favoring the development of potential drugs for autoimmune diseases including MG.<sup>42,43</sup> A deeper insight into the virus-host interactions, as well as evaluation of the immunological property of thymoma patients infected with virus, will pave the way for reliable preventive and therapeutic approaches for autoimmune diseases. With more awareness of the importance of viral infection in the development of thymic tumors such as thymoma and related diseases, the clinical and therapeutic usefulness of this opportunistic risk factor will be demonstrated.

## DISCUSSION

Thymomas always develop from the dysregulation of thymic epithelial cells, and which are usually connected to systemic diseases such as Good's syndrome and myasthenia gravis. In this review, we summarize the recent studies concerning the association between viral infection and thymoma development, as well as the autoimmune diseases related to thymoma. According to the studies on environmental risk factors for thymoma, herpesviruses are the best characterized, including CMV, EBV and HSV. The occurrence of thymoma is frequently reported in cases with CMV retinitis

or CMV encephalitis, and hypogammaglobulinemia were identified in most of these patients. By application of a molecular detection approach, several groups reported thymoma patients with immunodeficiency combined with HSV-1 or HSV-2 infection. Epstein-Barr virus was discovered in more investigations reporting its relationship with thymic tumors such as thymoma. It has previously been proposed that various molecules, which engage in immune response and inflammation, are positively or negatively associated with EBV-infected thymoma patients. The EBV latent proteins, LMP-1 and EBNA-1, have been demonstrated to interact with cellular proteins to affect the progression of EBV-associated lymphomas.<sup>69</sup> There are four distinct panels of EBV latent gene expression termed latency type III, II, I, and 0. Type II latency was indicated for EBV to initiate latent infection in thymus in a patient with MG.<sup>48</sup>

Although an increasing number of reports have implied that there is an association between viral infection with thymoma and other thymic tumors, the etiological role of the virus in the development of these diseases is still controversial. There have been distinctions in the detection rate from different laboratories, which may due to sample preparation, detection methods, statistical strategies or geographic factors. To what extent these viruses are involved in the occurrence of thymic tumors such as thymoma is unclear and needs further investigation. Hence, more evidence is necessary for a better understanding of whether viral infection is directly associated with thymoma pathogenesis. Based on previously published studies, viral infection may not play a major role, but could act as a participator during the development and progression in patients with thymoma. Moreover, the research on viral-infected thymoma and related thymic disease may highlight potential applications in clinical practice in three ways. First, whether there has been viral infection is probably an indicator of certain immune dysregulation with thymoma. For example, it has been previously reported that the early detection of CMV may be necessary in the identification of thymoma-associated autoimmune retinopathy. Thymoma patients with primary immunodeficiency are more susceptible to neurological opportunistic infection by the herpes simplex virus. Thus evaluation of HSV infection and thymoma in the early diagnosis of immunodeficient patients should be considered. Second, there are a subset of patients with thymic diseases susceptible to viral infections. The correlation of lymphoepithelioma-like thymic carcinoma with EBV may be limited to young Asians according to previously reported cases, while western patients have shown low prevalence of EBV infection in various histological types of thymoma.<sup>70,71</sup> Screening of such a susceptible population will be helpful in their early treatment and improve prognosis. Third, some thymoma patients accompanied by viral infection may benefit from antiviral therapy or in combination with thymectomy, demonstrating the treatment against virus is probably an alternative strategy for patients with thymic diseases. The onset of autoimmune diseases could be influenced by diverse environmental factors inclusive of pathogens such as viruses.

There have been investigations indicating the regulation of autoimmunity development by viral infection, which may contribute to autoantibody production and promote autoimmunity in patients. In a previous study, an increased level of anti-EBNA-1 antibodies was observed in multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus and MG,<sup>50</sup> which suggest that these autoimmune diseases may develop after a viral infection. More evidence of a viral etiology in autoimmune diseases is implicated by the observation of an antiviral response, especially dysregulation of interferons and interleukins.

The hypothesis that viral infection is involved in the pathogenesis of AIDs has been suggested because the thymus is sensitive to infection by virus. Viruses are potential triggering factors leading to immune dysregulation or autoimmunity in patients with thymoma and related diseases. In view of the high incidence of autoimmune diseases in thymoma patients, an inflammatory microenvironment may be induced to prime or sustain an autoimmune response by viral infection.<sup>27</sup> For instance, viral infection could trigger TLR3 signaling and interferon-I to enhance proinflammatory cytokine, therefore resulting in the development of thymoma-related MG.<sup>72,73</sup> MG might develop after EBV infection in some thymoma patients, thus EBV could probably promote autoimmunity through virus-host interactions and contribute to pathogenesis of MG with thymoma.<sup>49</sup> These data provide further evidence that pathogenesis of autoimmune diseases in thymoma patients may be related to a viral infection. The underlying mechanism of viral infection in thymoma-associated autoimmune diseases is poorly understood, but the change of inflammation in host cells could play a role in thymic abnormalities and immunity disorder due to this risk factor. Both the establishment of cell lines that originate from thymoma samples of myasthenia gravis patients, and the application of humanized mice to study thymic diseases induced by HTLV-I, are valuable tools for investigating the molecular basis of HTLV-I/II infection and oncogenic transformation.<sup>74,75</sup> Therefore a suitable animal model may shed light on analyzing virus-induced AIDs with thymoma in humans.

In conclusion, the presence of virus in thymoma patients with related diseases suggests a unique mechanism that is still not completely understood. Viral infection appears to play an important role in the pathogenesis of AIDs patients with thymoma or other thymic diseases. How these risk factors trigger autoimmunity and lead to immune disorders in thymoma remains to be investigated. With further studies conducted to reveal the involvement of viral infection and a better elucidation of thymoma and AIDs development, new methods on antiviral therapeutic strategy may be applied for the benefit of patients.

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#### CONFLICT OF INTEREST

No authors report any conflict of interest.

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