Pathology of Infectious Esophagitis: A Histopathologic Study of 157 Cases

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Abstract
The aim of this study was to clarify the pathological features of infectious esophagitis. We studied 157 cases with infectious esophagitis (Candida, herpes simplex virus, cytomegalovirus, and Mycobacterium tuberculosis: 138, 12, 6, and 1 case, respectively). The following conclusions were obtained. Infectious focus of candida and herpes simplex virus is limited to the esophagus. On the other hand, cytomegalovirus involved multiple organs. Macroscopically, candidal esophagitis appeared as elevated yellow-white plaques. Herpes simplex virus and cytomegalovirus-induced esophageal lesions consisted of well-demarcated ulcers of varying size. Histologically, candidal organisms were identified in the stratified squamous epithelium of the esophageal mucosa. Foci demonstrating the cellular changes characteristic of herpetic infection were detected in the squamous epithelium. On the other hand, cytopathic effects associated with cytomegalovirus-infection were observed in the mesenchymal cells such as fibroblasts and small vascular endothelial cells. We conclude that for the pathological diagnosis of infectious esophagitis, careful detection of the presence or absence of cytopathologic findings that are characteristic of each infectious disease is important in addition to referring to clinical information such as the underlying disease or drug history.

Key words: Infectious esophagitis, Diagnostic pathology

Introduction
A disease in which the esophagus is infected by a pathogen is referred to as an esophageal infection. The focus is generally associated with inflammation, and the disease is therefore histopathologically termed infectious esophagitis. Infectious esophagitis is classified into bacterial esophagitis, fungal esophagitis, and viral esophagitis according to the causal pathogen. In this study, on the basis of the analysis of gross appearance, histology, and clinical information of 157 cases clinicopathologically diagnosed as infectious esophagitis, we tried to extract pathomorphological images of infectious esophagitis and differential points per pathogen. In addition, we discuss morphologic changes observed in virally infected cells and the optimal biopsy site contributing to histopathological diagnosis of infectious esophagitis.

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Materials and Methods

Patients

Among esophageal biopsy tissues obtained from a total of 8208 cases that were detected histopathologically in the Department of Pathology, Fukuoka University Faculty of Medicine from January 2001 to the end of July 2016, 152 cases clinicopathologically diagnosed as infectious esophagitis plus 5 autopsy cases, 157 cases in total, were used as materials. Each of the biopsy and autopsy tissues was immersed and fixed in formalin, embedded in paraffin, cut into 4-μm sections, and stained with hematoxylin and eosin (HE) to create specimens.

This retrospective study protocol was approved by the Fukuoka University Medical Ethics Review Board (Approval Number 16-11-07).

Detection and identification of pathogens

Mycobacterium tuberculosis (M. tuberculosis) was detected and identified with Ziehl-Neelsen stain, and fungi were detected and identified with periodic acid-Schiff (PAS) reaction. For herpes simplex virus and cytomegalovirus, the presence or absence of inclusion bodies and multinucleated giant cells was detected in HE-stained specimens and identified immunohistochemically using marketed antibodies against each viral antigen.

Age, sex, underlying disease and drug history

Request forms for biopsy diagnosis and patient medical records were consulted, and age, sex, underlying disease, drug history, and bedridden condition of the patients were compiled. It should be noted that we mainly researched underlying diseases and drugs having immunosuppressive effects.

Distribution and gross appearance of the lesions

The distribution of lesions in the esophagus and other organs was estimated by imaging studies (e.g. esophagogastroduodenoscopy, colonoscopy, and computed tomography) and investigated by consulting the pathology diagnostic reports of the autopsy cases. Next, the gross appearance of each lesion was described through an overview of photographs taken during endoscopy and macroscopic images of the excised organs on which autopsy was performed.

Cytohistologic findings of the lesions

Cytohistologic findings observed in the HE-stained specimens were described.

Results

Pathogen types (Table 1)

Pathogen types included Candida (138 cases), herpes simplex virus (12 cases), cytomegalovirus (6 cases), and M. tuberculosis (1 case).

Age, sex, underlying disease, and drug history (Table 1)

Age and sex distributions were as follows: 26 to 93 years old; 128 men and 29 women. Number for men and women per pathogen were as follows: Candida, 111 men and 27 women; herpes simplex virus, 11 men and 1 woman; cytomegalovirus, 5 men and 1 woman; and M. tuberculosis, 1 man.

In particular, the rates of bedridden elderly people, malignant neoplasms (all cases were treated with anticancer agents), and steroid therapy were high, and the infection was followed by poorly controlled type 2 diabetes mellitus (HbA1c > 7.0%). Most bedridden elderly people developed advanced dementia or cerebrovascular disorders, and most malignant neoplasms included hematologic malignancies (24 cases) such as leukemia, lymphoma, and myeloma, and carcinomas of the digestive organ origin (9 cases) or pulmonary origin (4 cases). Additionally, all of the patients with acquired immunodeficiency syndrome (5 cases) and those with gastrostomy (18 cases) had complicated intractable candidiasis. Based on our search, one patient with esophageal tuberculosis, which was the least frequent condition, had pulmonary tuberculosis.

In terms of the above-mentioned drug history, anticancer agents accounted for the majority of the drugs used, followed by corticosteroid preparations for such autoimmune diseases as systemic lupus erythematosus and mixed connective tissue disease, as well as bronchial asthma and glomerulonephritis, and immunosuppressive agents after organ transplantation. Furthermore, among the 157 cases, 4 were healthy subjects defined as immunocompetent hosts with infectious esophagitis.

Distribution of the lesions (Table 2)

When the lesions were roughly classified according to organ type of focal distribution, one group was confined to the esophagus and the other group extended to other organs (the group with lesions formed in organs other
Table 1.  History of underlying disease and medication in 157 cases with infectious esophagitis

<table>
<thead>
<tr>
<th>Patient condition</th>
<th>Candida n = 138</th>
<th>Herpes simplex virus n = 12</th>
<th>Cytomegalovirus n = 6</th>
<th>Mycobacterium tuberculosis n = 1</th>
<th>Total No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedridden elderly *</td>
<td>53</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>54 (34.4)</td>
</tr>
<tr>
<td>Healthy subject **</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>4 (2.5)</td>
</tr>
<tr>
<td>Organ transplantation</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>5 (3.2)</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>28</td>
<td>5</td>
<td>4</td>
<td>0</td>
<td>37 (23.6)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>12 (7.6)</td>
</tr>
<tr>
<td>Acquired immunodeficiency syndrome</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5 (3.2)</td>
</tr>
<tr>
<td>Autoimmune disease</td>
<td>14</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>16 (10.2)</td>
</tr>
<tr>
<td>Bronchial asthma</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>9 (5.7)</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>7</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>10 (6.4)</td>
</tr>
<tr>
<td>Cushing syndrome</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>4 (2.5)</td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Chronic hepatitis C and liver cirrhosis</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4 (2.5)</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticancer agents</td>
<td>28</td>
<td>5</td>
<td>4</td>
<td>0</td>
<td>37 (23.6)</td>
</tr>
<tr>
<td>Steroid therapy †</td>
<td>28</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>31 (19.7)</td>
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<tr>
<td>Immunosuppressive therapy</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>5 (3.2)</td>
</tr>
</tbody>
</table>

Parentheses indicate percentage; and n, total number of cases. *: Including 18 patients with gastrostomy. **: Healthy subject defined as immunocompetent host with infectious esophagitis. †: Corticosteroid preparations not only including steroid pulse therapy but also low-dose inhaled steroid therapy.

Table 2.  Distribution of infectious foci in 157 cases with infectious esophagitis

<table>
<thead>
<tr>
<th></th>
<th>Candida n = 138</th>
<th>Herpes simplex virus n = 12</th>
<th>Cytomegalovirus n = 6</th>
<th>Mycobacterium tuberculosis n = 1</th>
<th>Total No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited to esophagus</td>
<td>114</td>
<td>10</td>
<td>1</td>
<td>0</td>
<td>125 (79.6)</td>
</tr>
<tr>
<td>Esophagus and other organs</td>
<td>24 *</td>
<td>2</td>
<td>5</td>
<td>1 **</td>
<td>32 (20.4)</td>
</tr>
</tbody>
</table>

Parentheses indicate percentage; and n, total number of cases. *: Including 22 patients with oropharyngeal involvement. The entire gastrointestinal tract was involved in a scattered distribution of small ulcers in 2 patients and one of them with disseminated candidiasis. **: Esophageal involvement as a result of extension from affected mediastinal lymph nodes associated with pulmonary tuberculosis.

than the esophagus), and the total is shown in Table 2. In both groups, multiple lesions of the infected esophagus were also present.

The lesions of candidal infection were confined to the esophagus in 114 cases (82.6%) and distributed dominantly in the mid to the lower esophagus rather than the upper esophagus. In contrast, 24 cases (17.4%) extended to other organs (e.g. oral cavity, tongue, and pharyngeal mucosa). Furthermore, 2 cases extended to the entire gastrointestinal tract and in one case, lesions spread to the systemic organs, resulting in a state of disseminated candidiasis.

The lesions of herpes simplex virus infection were confined to the esophagus in 10 cases (83.3%), and all lesions formed predominantly in the lower esophagus. In the remaining 2 cases (both autopsy cases), lesions also formed in the pharynx and the oral mucosa.

The lesions of cytomegalovirus infection were confined to the esophagus only in one case. In contrast, the remaining 5 cases (83.3%) extended to the entire gastrointestinal tract. In 2 of these latter 5 cases, autopsy revealed that lesions had also formed in various organs such as lung, adrenal gland, kidney, liver, pancreas, thyroid, and urinary bladder. All of the esophageal lesions were distributed predominantly in the mid to lower esophagus.

The lesions of M. tuberculosis formed in the lung and

Infectious esophagitis (Nimura et al.)
mediastinal lymph nodes as well as the mid esophagus. The lesions in the esophagus had adhered tightly to caseous lymph nodes in the mediastinum at several points and caused multiple esophageal ulcers.

**Gross appearances of the esophageal lesions**

The lesions of candidal infection varied from those recognized as millet- or rice grain-sized solitary lesions in the mucosal surface to those caused by their fusion and expansion. The former was often observed in the mild cases, and the latter often in the advanced cases. In the mildest cases, small white or yellowish-white mossy nodules were scattered or were present longitudinally in the mid to lower esophagus (Figures 1A, B). These small nodules were fixed to the mucosa, and they were difficult to detach by washing. In addition, the small nodules formed small unstained areas by Lugol’s iodine staining and were not densely stained (Figure 1C). In contrast, primarily in the advanced cases, a markedly fused and enlarged mossy substance exhibited a meringue-like gross appearance (Figure 1D). Furthermore, a dirty mossy substance adhered to the periclinal area of the

![Figure 1](image1.png)

**Figure 1** Endoscopic view of candidal esophagitis.
A few elevated white plaques up to 2mm in size (A). Many elevated white plaques greater than 2mm in size (B). Many well-demarcated unstained areas are observed after Lugol’s iodine staining (C). Many confluent white plaques mimicking meringue (D). Multiple elevated white plaques with hyperemia and hemorrhagic ulcer (E). The mesopharyngeal mucosa is thickly coated with numerous confluent plaques (F).

![Figure 2](image2.png)

**Figure 2** Endoscopic view of herpetic esophagitis.
Some discrete and shallow ulcers are seen in the middle thoracic esophagus. These ulcers have white or yellow raised margins (arrows) (A). Although some ulcers become confluent, these remain sharply demarcated (B). Multiple small-sized vesicular lesions are also seen in the mesopharyngeal mucosa (C).
Infectious esophagitis (Nimura et al.)

ulceration sites, which were accompanied by hyperemia and bleeding (Figure 1E). There was a sharp border between the site and the surrounding mucosa. In the cases of acquired immunodeficiency syndrome and gastrostomy, the whole mucosa from the pharynx to the lower esophagus was covered with a pseudomembranous mossy substance (Figure 1F).

The lesions of herpes simplex virus infection varied from those recognized as small round well-defined erosions, which often occurred in the mucosal surface, to erosions or ulcers with irregular-shaped borders that were formed by partial fusion and expansion (Figures 2A, B). Also, adhesion of exudates or bleeding was remarkable at the bottom of the ulcer as ulceration progressed, but the ulcer was almost shallow. Multiple small vesicular lesions up to 3mm in size were detected in the oropharyngeal mucosa (Figure 2C).

The lesions of cytomegalovirus infection formed multiple punched-out ulcers with a clear-cut boundary in all cases (Figure 3A). Among these ulcers, the larger ones tended to form along the longitudinal axis of the esophagus, and exudates adhered to the bottom of the ulcers to varying degrees and formed a rough surface. Further, due to the tendency to bleed in the cases with severe myelosuppression, bleeding from the bottom of the ulcer was remarkable. Shape of duodenal ulcer associated with cytomegalovirus infection was similar to that of esophagus (Figure 3B).

The lesions of *M. tuberculosis* infection were all found in the ruptured sites of esophageal lesions infected with lymph node tuberculosis (Figure 4A). In this study, caseous lesions were recognized in the inferior lobe of isolated lung at autopsy and rice grain-sized secondary lesions were often found in the surrounding areas (Figure 4B).

**Cytohistologic findings of the esophageal foci**

The lesions of *Candida* infection were associated with inflammatory cell infiltration by neutrophils or lymphocytes to varying degrees, and a fungal structure was found in the same sites (Figure 5A). *Candida* was stained reddish violet by PAS reaction, and pseudohyphae exhibiting a sausage-like shape and oval-shaped spores became clear (Figure 5B). In almost all cases, *Candida* hyphae penetrated from the most superficial layer into the stratified squamous epithelia, and in the sites of slightly deeper ulceration, invasion into the small blood vessels by *Candida* hyphae was also observed on photomicrographs.

The lesions of herpes simplex virus infection were found in stratified squamous epithelia that had degenerated or was in a state of coagulative necrosis. In contrast to the gross impression described above, the border between the foci and non-foci in the stratified squamous epithelia was clear, and the ulcers were shallow (Figure 6A). In the autopsy cases, lesions were also found in the ductal epithelium, which was connected with the submucosal esophageal glands. The cytohistologic findings observed in all cases were swelling of epithelial cells that contained...
intranuclear inclusion bodies, loss of connectivity between epithelial cells (corresponding to acantholysis) and subsequent bullous fissure formation, and the appearance of epithelial multinucleated giant cells (Figures 6B, C). The morphology of the observed intranuclear inclusion bodies varied from those of a ground-glass appearance to those surrounded by a ring-shaped halo. However, cytoplasmic inclusion bodies were not recognized in any cases. When the esophageal tissues isolated at autopsy were examined in detail, obvious intranuclear inclusion bodies were not found in the mesenchymal cells such as fibroblasts or small vascular endothelial cells of the lesions. The previously described intranuclear inclusion bodies were not only labeled with anti-herpes simplex virus type 1 antibody (Figure 6D) but also type 2 antibody. Thus, immunohistochemistry using formalin-fixed paraffin section could not distinguish the serotype of the herpes simplex virus.

The lesions of cytomegalovirus infection could be found in mesenchymal cells (e.g. fibroblasts or small vascular
**Figure 6** The histological features of herpetic esophagitis.

Low-power view of the lesion shown in an adult patient with lymphoblastic leukemia. The small-sized erosion (arrows) does not extend through the muscularis mucosae (A). Center of esophageal erosion, showing markedly degeneration and coagulative necrosis of epithelial cells, some of which contain characteristic inclusions within nuclei. Nucleus of epithelial cell has Cowdry type A inclusion (arrows), which is deeply acidophilic and centrally placed with surrounding halo. Intracytoplasmic inclusions are not detected in any epithelial cells. Some epithelial cells are multinucleated and the nuclei are molded to one another (B). Margin of esophageal erosion, showing moderate degeneration of epithelial cells. Many nuclei have amphiphilic to basophilic inclusions with ground-glass appearance. Small-sized vesicles (arrows) are formed as a result of acantholysis (C). Immunohistochemical stain for herpes simplex virus type 1, highlighting many intranuclear inclusions (D).

endothelial cells) at the bottom of the erosion or ulcer (Figure 7A). The cytohistologic findings observed in all cases were the appearance of large cells having inclusion bodies not only in the nucleus but also in the cytoplasm. In the high-power fields, intranuclear inclusion bodies surrounded by a ring-shaped halo, which is referred to as a "owl’s-eye inclusion," as well as cytoplasmic inclusion bodies were observed (Figure 7B).

Also, in 2 autopsy cases, flask-shaped ulcers formed that extended deep into the submucosal tissue (Figure 7C). In the small vessels that were distributed in the bottom of the ulcer, the appearance of necrosis accompanied by fibrin deposits was occasionally found. In addition, in the stratified squamous epithelium of the lesions, a cytopathic appearance such as that observed in the lesions of herpes simplex virus was not found.

The tuberculous esophageal ulcer was found uniformly in the site of fistula formation between the caseous lymph node and the esophagus (Figure 8A). The lesion of the esophageal wall and the lymph node were comprised of epithelioid cell granulomas, which were mixed with Langhans-type multinucleated giant cells, and were accompanied by areas of coagulation necrosis in a variety of sizes in the center (Figures 8B, C). Also, in the area of coagulation necrosis in the lesion, many rod-shaped bacteria stained red by acid-fast bacilli staining were observed (Figure 8D).
Figure 7  The histological features of cytomegalovirus-induced esophageal ulcer.

Many inclusion-bearing stromal cells are seen in the deepest portion of the esophageal ulcer. The ulcer base contains acute and chronic inflammatory cells, varying amounts of fibrin, and necrotic debris. Anti-cytomegalovirus immunostaining highlights the intranuclear inclusions (inset) (A). Characteristic cytopathic effects associated with cytomegalovirus-infection. Enlargement ("cytomegalic change") of the virus-infected stromal cells; a prominent large, oval intranuclear inclusion with peripheral margination of the nuclear chromatin, producing a clear halo around the inclusion; and less-well-defined fine-granular intracytoplasmic inclusions (arrows) (B). Low-power view of the sharply demarcated ulcer an adult patient with non-Hodgkin B-cell lymphoma. The ulcer is deep and its cut-surface shows flask-shaped appearance (arrows) (C).

Discussion

The heavy use of anticancer agents, immunosuppressive agents, corticosteroid preparations, and antibiotics has recently changed the face of infection. If the immune mechanisms of a host are impaired or disrupted, the fungi, viruses, and M. tuberculosis that have been mentioned in this study, can injure the various organs as opportunistic pathogens, and when the symptoms become severe, they can threaten the life of the host. Therefore, to diagnose and treat each infectious disease properly and rapidly, an understanding or grasp of not only these pathologic images but also the clinical characteristics such as underlying disease and drug history is necessary. 1)

Here, our ultimate goal was to obtain pathological findings and patient backgrounds that contribute to the diagnosis of infectious esophagitis, and we analyzed the gross appearance, histology, and clinical information of 157 cases including autopsy cases.

Based on the organ distribution of the lesions, many cases of Candida and herpes simplex virus were localized to the esophagus, whereas in a few cases, pathogens spread to organs other than the gastrointestinal tract. For cytomegalovirus, however, only a single case was localized to the esophagus, and all of the other cases had formation in the gastrointestinal tract or various systemic organs, which indicated that the organ distribution of cytomegalovirus was in contrast to that of the other two infections. The results nearly corresponded to those of past reports. 2,3)

From the viewpoint of gross appearance, yellowish-white mossy nodules caused by Candida proliferation varied from an isolated millet-sized nodule to a larger nodule caused by fusion. The small whitish lesion was similar to glycogenic acanthosis at first glance, but it was not densely stained by Lugol’s iodine staining and differentiation was easy. 4) Viral esophagitis was characterized by the form and size of the erosion or ulcer. Herpes simplex virus tended to form small round erosions that were fused. The surrounding mucosa of the fused erosion was inevitably accompanied by small round erosions (so-called satellitosis). 3,5) Cytomegalovirus,
The histological features of esophageal tuberculosis. Figure 8

Low-power view of esophageal ulcer shown in Figure 4A. Modified Masson’s trichrome method (A). Epithelioid cell granuloma surrounded by a cuff of lymphocytes and plasma cells is also seen in the lamina propria mucosae of the esophagus (arrows). Several Langhans’ giant cells are intermingled (B). Note the granuloma with caseation necrosis (※) surrounded by aggregations of epithelioid cells and giant cells in the mediastinal lymph node (C). Numerous linear to curvilinear acid-fast bacilli in the caseous center of the lesion (D).

However, tended to form a large-diameter punched-out ulcer, and satellitosis was unremarkable in the surrounding mucosa. 

From the viewpoint of histology, Candida and herpes simplex virus mainly infected the stratified squamous epithelia, whereas cytomegalovirus infected mesenchymal cells such as fibroblasts or small vascular endothelial cells. According to the results, the affinity to host cells obviously differed with the type of pathogen, which was thought to be the major cause of the difference in the gross appearance of the esophageal lesions. Because herpes simplex virus directly injures epithelial cells of the esophageal mucosa, ulcers at such lesion sites were shallow. In contrast, cytomegalovirus directly injured small vascular endothelial cells that were distributed in the esophageal mucosal or submucosal tissue and eventually caused ischemia of the vascular bed, therefore suggesting that an ulcer at this type of lesion site was deeper and much wider than that at a lesion site of herpes simplex virus infection. For herpes simplex virus, inclusion bodies were observed in the nucleus, whereas for cytomegalovirus, inclusion bodies were observed in both the nucleus and the cytoplasm, indicating that the formation sites of inclusion bodies in the infected cells differed with the type of virus. Thus, by considering the difference in affinity to the host cells or the formation site of inclusion bodies, it might be possible to estimate the causative virus in HE-stained specimens. Further, when considering the optimal biopsy site to obtain these pathological findings, it is the mossy raised area (e.g. ...
white or yellowish-white plaques) for *Candida*, the central area of the erosion (e.g. sloughed mucosa) or the border of the surrounding mucosa for herpes simplex virus, and from the bottom of the ulcer (e.g. granulation tissue) for cytomegalovirus.

According to the patients’ information, except for the 4 healthy subjects, most patients had some sort of underlying disease, and elderly bedridden people along with those with malignant neoplasms accounted for a large percentage, followed by those with poorly controlled diabetes. Further, in terms of drug history, a large percentage of the drugs used comprised anticancer agents, corticosteroid preparations, and immunosuppressive agents, which was the major factor in reducing the host’s resistance to infection. Additionally, some patients with oro-pharyngeal and esophageal candidiasis had received "low-dose" inhaled steroid therapy for bronchial asthma.

Finally, in the single case of tubercular esophageal ulcer, the route of infection and the gross appearance were almost the same as those in past reports.\(^6\)

We conclude that for the pathological diagnosis of infectious esophagitis, careful detection of the presence or absence of cytohistologic findings that are characteristic of each infectious disease is important in addition to referring to clinical information such as the underlying disease or drug history.

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