Hematology

Review (Narrative)

Hodgkin’s Lymphoma: From A to Z facts

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SUMMARY

Hodgkin lymphoma is an uncommon cancer that develops in the lymphatic system, which is a network of vessels and glands spread throughout your body. The lymphatic system is part of your immune system. Clear fluid called lymph flows through the lymphatic vessels and contains infection-fighting white blood cells, known as lymphocytes. In Hodgkin lymphoma, B-lymphocytes (a particular type of lymphocyte) start to multiply in an abnormal way and begin to collect in certain parts of the lymphatic system, such as the lymph nodes (glands). The affected lymphocytes lose their infection-fighting properties, making you more vulnerable to infection. The most common symptom of Hodgkin lymphoma is a painless swelling in a lymph node, usually in the neck, armpit or groin. In this review, we will present the facts of Hodgkin lymphoma in detail to show the current development in understanding the disease and every aspect of its genesis and treatment.

KEYWORDS

Hodgkin lymphoma; Immunity; Neoplasm; Therapy; Outcomes


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INTRODUCTION

Hodgkin disease (Hodgkin lymphoma) is a type of lymphoma, a cancer that starts in white blood cells called lymphocytes (1). Lymphocytes are part of the immune system. Cancer starts when cells in the body begin to grow out of control. Cells in nearly any part of the body can become cancer, and can spread to other areas of the body. Hodgkin’s disease (HD) primarily arises within the lymph nodes and involves the extra nodal sites secondarily. This group comprises about 8% of all cases of lymphoid neoplasm. The incidence of the disease has bimodal peaks—one in young adults between the age of 15 and 35 years and the other peak after 5th decade of life. The HD is more prevalent in young adult males than females. The classical diagnostic feature is the presence of Reed-Sternberg (RS) cell (or Dorothy-Reed-Sternberg cell (2, 3).

A history of infectious mononucleosis due to infection by Epstein-Barr virus (EBV) may increase risk of HL, but the precise contribution of EBV remains largely unknown. Hodgkin lymphoma is characterized by the orderly spread of disease from one lymph node group to another and by the development of systemic symptoms with advanced disease. When Hodgkins cells are examined microscopically, multinucleated Reed-Sternberg cells (RS cells) are the characteristic histopathologic finding (4).

Hodgkin lymphoma may be treated with radiation therapy, chemotherapy, or hematopoietic stem cell transplantation, with the choice of treatment depending on the age and sex of the patient and the stage, bulk, and histological subtype of the disease. The overall five-year survival rate for adults in the United States for 2004-2010 is 85% (5). For children and adolescents (2003-2009), the five-year survival rate is 97% (6). There have been many cases of individuals living over 40 years after diagnosis. However, few studies follow people living for periods as long as 25 years, and those studies are of older treatments with more life-threatening adverse effects. There is insufficient data available about the long-term outcomes of newer, less-toxic regimens and ones which limit radiation exposure. Radiation treatments, and some chemotherapy drugs, pose a risk of causing potentially fatal secondary cancers, heart disease, and lung disease 40 or more years later. Modern treatments greatly minimize the chances of these late effects (7).

The disease occurrence shows two peaks: the first in young adulthood (age 15–35) and the second in those over 55 years old (8). It was named after the English physician Thomas Hodgkin, who first described abnormalities in the lymph system in 1832.

EPIDEMIOLOGY

Hodgkin lymphoma can develop at any age, but it mostly affects young adults in their early 20s and older adults over the age of 70. Slightly more men than women are affected. Around 1,900 people are diagnosed with Hodgkin lymphoma in the UK each year (9). You also have an increased risk of developing Hodgkin lymphoma if a first-degree relative (parent, sibling or child) has had the condition.

PATHOGENESIS

Hodgkin lymphoma is a neoplasm characterized by the presence of clonal malignant Hodgkin/Reed-Sternberg (HRS) cells in a reactive cellular background comprised of variable numbers of granulocytes, macrophages, plasma cells, and lymphocytes (10). Historically, HRS cells have been enigmatic and difficult to study, as they often constitute less than 1 percent of the cells in involved tissues. The central pathogenic issues in Hodgkin lymphoma are: the origin of HRS cells, the identity of the events underlying the transformation of HRS cells, and the nature of the signals that produce the intense, characteristic tissue response.

The mystery of the origin of HRS cells was ultimately solved by elegant molecular studies that relied on single cell micromanipulation of HRS cells, coupled with amplification of RNA and genomic DNA by the polymerase chain reaction (PCR). These techniques established a B cell origin for HRS cells in the vast majority of cases of HL and led to the identification of recurrent molecular abnormalities in HRS cells (11).

CLASSIFICATION

Types of Hodgkin disease

Different types of Hodgkin disease are classified by how they look under the microscope. This is important because types of Hodgkin disease may grow and spread differently and may be treated differently. All types of Hodgkin disease are malignant (cancerous) because as they grow they can invade and destroy normal tissue and spread to other tissues. The 2 main types are (12):

- Classic Hodgkin disease
- Nodular lymphocyte predominant Hodgkin disease

Classic Hodgkin disease

Classic Hodgkin disease (HD) accounts for about 95% of all cases of Hodgkin disease in developed countries. The cancer cells in classic HD are called Reed-Sternberg cells (after the 2 doctors who first described them). These cells are usually an abnormal type of B lymphocyte. Reed-Sternberg cells are much larger than normal lymphocytes and also look different from the cells of non-Hodgkin lymphomas and other cancers.
Review

The enlarged lymph nodes in classic HD usually have a small number of Reed-Sternberg cells and a large number of surrounding normal immune cells. It is mainly these other immune cells that account for the enlarged lymph nodes. Classic Hodgkin lymphoma has 4 subtypes:

- **Nodular sclerosis Hodgkin disease**
  
  Is the most common subtype and is composed of large tumor nodules showing scattered lacunar classical RS cells set in a background of reactive lymphocytes, eosinophils and plasma cells with varying degrees of collagen fibrosis/sclerosis. This is the most common type of Hodgkin disease in developed countries, accounting for about 40% to 60% of cases. It is most common in teens and young adults, but it can occur in people of any age. It tends to start in lymph nodes in the neck or chest. It is characterised by two essential features:
  
  - Bands of collagen: Variable amount of fibrous tissue is characteristically present in the involved lymph nodes. Occasionally, the entire lymph node may be replaced by dense hyalinised collagen.
  
  - Lacunar type RS cells: Characteristic lacunar type of RS cells with distinctive pericellular halo are present. These cells appear lacunar due to the shrinkage of cytoplasm in formalin-fixed tissue. The pericellular halo is not seen if the tissue is fixed in Zenker’s fluid. In addition to these 2 characteristics, the nodules between the fibrous septa consist predominantly of lymphocytes and macrophages, sometimes with foci of necrosis.

- **Mixed cellularity Hodgkin disease**
  
  This is the second most common type (15% to 30%) and is seen mostly in older adults (although it can occur at any age). It can start in any lymph node but most often occurs in the upper half of the body. Is a common subtype and is composed of numerous classic RS cells admixed with numerous inflammatory cells including lymphocytes, histiocytes, eosinophils, and plasma cells without sclerosis. This type is most often associated with EBV infection and may be confused with the early, so-called 'cellular' phase of nodular sclerosing CHL. This form of HD generally replaces the entire affected lymph nodes by heterogeneous mixture of various types of apparently normal cells. These include proliferating lymphocytes, histiocytes, eosinophils, neutrophils and plasma cells. Some amount of fibrosis and focal areas of necrosis are generally present. Typical RS cells are frequent.

- **Lymphocyte-rich Hodgkin disease**
  
  This subtype accounts for about 5% of Hodgkin disease cases. It usually occurs in the upper half of the body and is rarely found in more than a few lymph nodes. Is a rare subtype, show many features which may cause diagnostic confusion with nodular lymphocyte predominant B-cell non-Hodgkin's Lymphoma (B-NHL) (13). This form also has the most favorable prognosis. The lymphocyte-predominance type of HD is characterized by proliferation of small lymphocytes admixed with a varying number of histiocytes forming nodular or diffuse pattern.
  
  - Nodular form is characterized by replacement of nodal architecture by numerous large neoplastic nodules.
  
  - Diffuse form does not have discernible nodules but instead there is diffuse proliferation of cells.

  However, currently nodular form of lymphocyte predominant HD has been categorized separately due to its distinct immune phenotyping features and prognosis. For making the diagnosis, definite demonstration of RS cells is essential which are few in number, requiring a thorough search. In addition to typical RS cells, polyploid variant having polyploid, and twisted nucleus (popcornlike) may be found in some cases. This type of HD usually does not show other cells like plasma cells, eosinophils and neutrophils, nor are necrosis or fibrosis seen (14).

- **Lymphocyte-depleted Hodgkin disease**
  
  This is the least common form of Hodgkin disease, making up less than 1% of cases. It is seen mainly in older people. The disease is more likely to be advanced when first found, in lymph nodes in the abdomen as well as in the spleen, liver, and bone marrow. Is a rare subtype, composed of large numbers of often pleomorphic RS cells with only few reactive lymphocytes which may easily be confused with diffuse large cell lymphoma. Many cases previously classified within this category would now be reclassified under anaplastic large cell lymphoma. In this type of HD, the lymph node is depleted of lymphocytes. There are two variants of lymphocyte-depletion HD:
  
  - Diffuse fibrotic variant is hypocellular and the entire lymph node is replaced by diffuse fibrosis, appearing as homogeneous, fibrillar hyaline material. The area of hyalinosis contains some lymphocytes, atypical histiocytes (Hodgkin cells), and numerous typical and atypical (pleomorphic) RS cells.
  
  - Reticular variant is much more cellular and consists of large number of atypical pleomorphic histiocytes, scanty lymphocytes and a few typical RS cells.

**Nodular lymphocyte predominant Hodgkin disease**

Nodular lymphocyte predominant Hodgkin disease (NLPHD) accounts for about 5% of Hodgkin disease. The cancer cells in NLPHD are large cells called popcorn cells (because they look like popcorn), which are variants of Reed-Sternberg cells.

NLPHD usually starts in lymph nodes in the neck and under the arm. It can occur in people of any age, and is more common in men than in women. Nodular lymphocyte predominant Hodgkin's lymphoma expresses CD20, and is not currently considered a form of classical Hodgkin's. For the other forms, although the traditional B cell markers (such as CD20) are not expressed on all cells (11), Reed–Sternberg cells are usually of B cell origin. Although Hodgkin's is now frequently grouped with other B cell lymphomas, the distinction between these 2 entities is maintained in the current World Health Organization classification of lymphoid neoplasms, and is based on expression of CD20, with Reed–Sternberg cells being negative for CD20 and NLPHD cells being positive for CD20.
cell malignancies, some T cell markers (such as CD2 and CD4) are occasionally expressed (14). However, this may be an artifact of the ambiguity inherent in the diagnosis. Hodgkin cells produce interleukin-21 (IL-21), which was once thought to be exclusive to T cells. This feature may explain the behavior of classical Hodgkin's lymphoma, including clusters of other immune cells gathered around HL cells (infiltrate) in cultures. This is a newly described entity which is distinct from the classic HD described above. This type was previously included in lymphocyte predominant type of Hodgkin lymphoma. Its peculiarities are as under:

- These cases of HD have a nodular growth pattern (similar to nodular sclerosis type).
- Like lymphocyte-predominant pattern of classic type, there is predominance of small lymphocytes with sparse number of RS cells.
- These cases of HD have distinctive immunophenotyping—CD45 positive, epithelial membrane antigen (EMA) positive but negative for the usual markers for RS cells (CD15 and CD30 negative).
- Though generally it has a chronic relapsing course, but some cases of this type of HD may transform into large B-cell NHL.

**REED-STERNBERG CELL**

The diagnosis of Hodgkin’s disease rests on identification of RS cells, though uncommonly similar cells can occur in infectious mononucleosis and other forms of lymphomas. Therefore, additional cellular and architectural features of the biopsy must be given due consideration for making the histologic diagnosis. There are several morphologic variants of RS cells which characterize different histologic subtypes of HD (15):

**Classic RS cells**

Classic RS cells are large cells which have characteristically bilobed nucleus appearing as mirror image of each other but occasionally the nucleus may be multilobed. Each lobe of the nucleus contains a prominent, eosinophilic, inclusion-like nucleolus with a clear halo around it, giving an owl-eye appearance. The cytoplasm of cell is abundant and amphiphilic.

**Lacunar type RS cell**

Lacunar type RS cell is smaller and in addition to above features has a pericellular space or lacuna in which it lies, which is due to artefactual shrinkage of the cell cytoplasm. It is characteristically found in nodular sclerosis variety of HD.

**Polyploid type RS cells**

Polyploid type RS cells are seen in lymphocyte predominance type of HD. This type of RS cell is larger with lobulated nucleus in the shape of popcorn.

**Pleomorphic RS cells**

Pleomorphic RS cells are a feature of lymphocyte depletion type. These cells have pleomorphic and atypical nuclei. The nature and origin of RS cells, which are the real neoplastic cells in HD, have been a matter of considerable debate.

One main reason for this difficulty in their characterization is that in HD, unlike most other malignancies, the number of neoplastic cells (i.e. RS cells) is very small (less than 5%) which are interspersed in the predominant reactive cells. In general, the number of RS cells is inversely proportional to the number of lymphocytes in a particular histologic subtype of HD. Immunophenotyping of RS cells reveals monoclonal lymphoid cell origin of RS cell from B-cells of the germinal centre in most subtypes of Hodgkin’s disease (16). RS cells in all types of Hodgkin’s diseases, except in lymphocyte predominance type, express immunoreactivity for CD15 and CD30. RS cells in lymphocyte predominance type, however, are negative for both CD15 and CD30, but positive for CD20. RS cells are invariably accompanied by variable number of atypical Hodgkin cells which are believed to be precursor of RS cells but are not considered diagnostic of HD. Hodgkin cells are large mononuclear cells (rather than mirror image nuclei) having nuclear and cytoplasmic similarity to that of RS cell.

**DIAGNOSTIC ABNORMALITIES**

**Hematologic Abnormalities**

A moderate, normocytic and normochromic anemia is often present.

- Serum iron and TIBC are low but marrow iron stores are normal or increased.
- Marrow infiltration by the disease may produce marrow failure with leucoerythroblastic reaction.
- Routine blood counts reveal moderate leukaemoid reaction.
  - Cases with pruritus frequently show peripheral eosinophilia.
  - Advanced disease is associated with absolute lymphopenia.
- Platelet count is normal or increased.
- ESR is invariably elevated.

**Immunologic abnormalities**

There is progressive fall in immunocompetent T-cells with defective cellular immunity. There is reversal of CD4:CD8 ratio and anergy to routine skin tests.

Humoral antibody production is normal in untreated patients until late in the disease.

**Staging**
Following biopsy and histopathologic classification of HD, the extent of involvement of the disease (i.e. staging) is studied in order to select proper treatment and assess the prognosis (17). Ann Arbor staging classification takes into account both clinical and pathologic stage of the disease.

For complete staging, a number of other essential diagnostic studies are recommended. These are as under:

- Detailed physical examination including sites of nodal involvement and splenomegaly.
- Chest radiograph to exclude mediastinal, pleural and lung parenchymal involvement.
- CT scan of abdomen and pelvis.

**Ann Arbor Staging Classification of HD**

- **Stage I:** Involvement of a single lymph node region
  (A or B) IE Involvement of a single extra-lymphatic organ or site.

- **Stage II:** Involvement of two or more lymph node
  (A or B) regions on the same side of the diaphragm.
  IIE (or) with localised contiguous involvement of an extranodal organ or site.

- **Stage III:** Involvement of lymph node regions on both sides
  (A or B) of the diaphragm.
  IIIE (or) with localised contiguous involvement of an extranodal organ or site.
  IIIS (or) with involvement of spleen.
  IIIES (or) both features of IIIE and IIIS.

- **Stage IV:** Multiple or disseminated involvement of one
  (A or B) or more extra-lymphatic organs or tissues with or without lymphatic involvement.
  (A = Asymptomatic; B = Presence of constitutional symptoms; E = Extranodal involvement; S = Splenomegaly).

**CLINICAL FEATURES**

Hodgkin’s disease is particularly frequent among young and middle-aged adults. All histologic subtypes of HD, except the nodular sclerosis variety, are more common in males. The disease usually begins with superficial lymph node enlargement and subsequently spreads to other lymphoid and non-lymphoid structures (18).

- Most commonly, patients present with painless, movable and firm lymphadenopathy. The cervical and mediastinal RS cells showing positive immunostaining for CD15, a B-cell marker. lymph nodes are involved most frequently. Other lymph node groups like axillary, inguinal and abdominal are involved sometimes.
- Approximately half the patients develop splenomegaly during the course of the disease. Liver enlargement too may occur.

- Constitutional symptoms (type B symptoms) are present in 25-40% of patients. The most common is low-grade fever with night sweats and weight loss. Other symptoms include fatigue, malaise, weakness and pruritus.

**RISK FACTORS**

A risk factor is anything that affects your chance of getting a disease such as cancer. Different cancers have different risk factors. Some cancer risk factors, like smoking, can be changed. Others, like a person’s age or family history, cannot be changed.

Scientists have found a few risk factors that make a person more likely to develop Hodgkin disease (although it’s not always clear why these factors increase risk). But having a risk factor, or even several, does not mean that you will definitely get the disease (19). And many people who get the disease may have few or no known risk factors. Even if a person with Hodgkin disease has one or more risk factors, it is often very hard to know how much these factors might have contributed to the lymphoma.

**Epstein-Barr virus infection/mononucleosis**

People who have had infectious mononucleosis (sometimes called mono for short), an infection caused by the Epstein-Barr virus (EBV), have an increased risk of Hodgkin disease. Although the risk is higher than for people who have not had mono, the overall risk is still very small.

The exact role of EBV in the development of Hodgkin disease is not clear. Many people are infected with EBV, but very few develop Hodgkin disease. Parts of the virus are found in Reed-Sternberg cells in about 1 out of 3 patients with Hodgkin disease. But the other people with Hodgkin disease have no signs of EBV in their cancer cells (20).

**Age**

People of any age can be diagnosed with Hodgkin disease, but it is most common in early adulthood (ages 15 to 40, especially in a person’s 20s) and in late adulthood (after age 55).

**Gender**

Hodgkin disease occurs slightly more often in males than in females.

**Geography**

Hodgkin disease is most common in the United States, Canada, and northern Europe, and is least common in Asian countries.

**Family history**

Brothers and sisters of young people with this disease have a higher risk for Hodgkin disease. The risk is very high for an identical twin of a person with Hodgkin disease. But a
family link is still uncommon – most people with Hodgkin disease do not have a family history of it.

It’s not clear why family history might increase risk. It might be because family members have similar childhood exposures to certain infections (such as Epstein-Barr virus), inherited gene changes that make them more likely to get Hodgkin disease, or some combination of these factors.

Socioeconomic status

The risk of Hodgkin disease is greater in people with a higher socioeconomic background. The reason for this is not clear. One theory is that children from more affluent families might be exposed to some type of infection (such as Epstein-Barr virus) later in life than children from less affluent families, which might somehow increase their risk.

HIV infection

The risk of Hodgkin disease is increased in people infected with HIV, the virus that causes AIDS.

TREATMENT

General treatment information

After Hodgkin disease is staged, the cancer care team will discuss treatment options with you. Treatment for Hodgkin disease is based largely on the stage of the disease. But other factors, including a person’s age and general health, and the type and location of the disease, might also affect treatment options (21).

For almost all patients with Hodgkin disease, cure is the main goal. But treatment can have side effects that often don’t show up for many years. Because of this, doctors try to choose a treatment plan with the lowest risk of possible side effects.

Several types of treatment can be used for Hodgkin disease:

- Chemotherapy
- Radiation therapy
- Immunotherapy
- High-dose chemotherapy and stem cell transplant

The two main ways of treating Hodgkin disease are chemotherapy and radiation therapy. Depending on the situation, one or both of these treatments might be used (22).

Immunotherapy and high-dose chemotherapy with stem cell transplants may be used for certain patients, especially if other treatments haven’t worked. Except for biopsy and staging, surgery is rarely used to treat Hodgkin disease. See “Treating classic Hodgkin disease by stage” or “Treating nodular lymphocyte predominant Hodgkin disease” for details on common treatment plans. See also “Treating Hodgkin disease in children” and “Hodgkin disease during pregnancy” for information about treatment in special circumstances.

Based on your treatment options, you may have different types of doctors on your treatment team. These doctors may include:

- A hematologist: a doctor who treats disorders of the blood, including lymphomas.
- A medical oncologist: a doctor who treats cancer with medicines.
- A radiation oncologist: a doctor who treats cancer with radiation therapy.

Chemotherapy (chemo) is the use of drugs to kill cancer cells (23). Chemotherapy for Hodgkin disease is usually injected into a vein under the skin or taken as a pill. Chemo drugs enter the bloodstream and travel throughout the body to reach and destroy cancer cells wherever they may be.

Chemotherapy for Hodgkin disease

Doctors give chemo in cycles, in which a period of treatment is followed by a rest period to give the body time to recover (24). Each cycle generally lasts for several weeks. Most chemo treatments are given on an outpatient basis (in the doctor’s office, clinic, or hospital outpatient department), but some may require a hospital stay.

The chemo regimens for Hodgkin disease combine several drugs because different drugs kill cancer cells in different ways. The combinations used to treat Hodgkin disease are often referred to by abbreviations. The most common regimen in the United States is a 4-drug combination called ABVD, which consists of:

- Adriamycin® (doxorubicin)
- Bleomycin
- Vinblastine
- Dacarbazine (DTIC)

Other common regimens include:

- BEACOPP
- BEACOPP
- Etoposide (VP-16)
- Adriamycin (doxorubicin)
- Cyclophosphamide (Cytoxan®)
- Oncovin® (vincristine)
- Procarbazine
- Prednisone
- Stanford V
- Doxorubicin (Adriamycin)
- Mechlorethamine (nitrogen mustard)
- Vincristine
- Vinblastine
- Bleomycin
- Etoposide
- Prednisone

Radiation is given after chemo in the Stanford V regimen, and it is sometimes given after the ABVD or BEACOPP regimens as well (25).

Other chemo combinations can also be used for Hodgkin disease. Most use some of the same drugs listed above, but they might include different combinations and be given on different schedules.
Side Effects
Chemo drugs attack cells that are dividing quickly, which is why they work against most types of lymphoma cells. But other cells in the body, such as those in the bone marrow (where new blood cells are made), the lining of the mouth and intestines, and the hair follicles, also divide quickly (26). These cells are also likely to be affected by chemotherapy, which can lead to side effects.

The side effects depend on the type and dose of drugs given and the length of time they are taken. They can include:

- Hair loss
- Mouth sores
- Loss of appetite
- Nausea and vomiting
- Diarrhea
- Increased chance of infections (from having too few white blood cells)
- Easy bruising or bleeding (from having too few blood platelets)
- Fatigue (from having too few red blood cells)

These side effects are usually short-lived and go away after treatment is finished. If serious side effects occur, the chemotherapy may have to be delayed or the doses reduced.

There are often ways to lessen these side effects. For example, drugs are usually given to help prevent nausea and vomiting.

Infections can be very serious in people getting chemo. Drugs known as growth factors, such as G-CSF (Neupogen®) or GM-CSF (Leukine®), are sometimes given to help the body make more white blood cells and thus reduce the chance of infection. Antibiotics may also be given at the earliest sign of an infection, such as a fever.

If your white blood cell counts are very low during treatment, you can help reduce your risk of infection by carefully limiting your exposure to germs. During this time, your doctor may advise you to:

- Wash your hands often.
- Avoid fresh, uncooked fruits and vegetables and other foods that might carry germs.
- Avoid fresh flowers and plants because they may carry mold.
- Make sure other people wash their hands before they come in contact with you.
- Avoid large crowds and people who are sick.

If your platelet counts are very low, you may be given drugs or platelet transfusions to help protect against bleeding. Fatigue caused by anemia (very low red blood cell counts) can be treated with drugs or with red blood cell transfusions.

Late or long-term side effects
Some chemo drugs can have long-lasting side effects, some of which might not occur until months or years after treatment has ended (27). For example:

- Doxorubicin can damage the heart, so your doctor may order tests to check your heart function before and during treatment with this drug.
- Bleomycin can damage the lungs, so some doctors order tests of lung function (called pulmonary function tests) before starting patients on this drug.
- Some chemo drugs can increase the risk of getting a second type of cancer later in life (such as leukemia), especially in patients who also get radiation therapy.
- In children and young adults, some chemo drugs can also affect body growth and fertility (ability to have children) later on.

ARTICLE INFORMATION

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