

Hodgkin's disease

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Abstract

Hodgkin disease (HD) is a malignant tumor characterized by pleomorphic lymphocytic and histiocytic infiltrate with multinucleated Reed-Sternberg cells. Childhood cancers represent only 2% of neoplasms affecting the general population and HD accounts for 5.5% of all pediatric cancers. The primary nodal site of HD is situated above the diaphragm in two-thirds of patients. The usual clinical presentation consists of painless cervical or supraclavicular adenopathy. Splenomegaly and hepatomegaly often indicate advanced disease. Systemic symptoms are typical of B symptoms, including fever, weight loss, and night sweats. Epstein-Barr Virus is likely to be pathologic agent in a HD subgroup, although it is not a necessary factor for the development of HD or supraclavicular adenopathy. Currently, almost all children receive combined chemotherapy with low dose irradiation (1500 - 2000 cGy) solely in the initially involved area. Overall survival is more than 90%. New therapeutic strategies targeting molecular mechanisms in HD are currently emerging. Children with HD should be referred to multidisciplinary teams in pediatric oncology units with experience in treating pediatric cancers.

Keywords

Hodgkin's disease; combined treatment; late effects; second tumors

Disease name and synonyms

- Hodgkin's disease (HD)
- Hodgkin's Lymphoma

(RS). Subsequently, throughout the 20th century, advances in the diagnosis and therapeutic fields contributed significantly to the management and prognosis of this disease.

Disease history

In 1832, Thomas Hodgkin provided the anatomic description of the disease (1). Sternberg, in 1898 and Reed (2), in 1902, identified the multinucleated giant cell, a pathognomic finding of the disease, known as Reed-Sternberg cell

Frequency

Although childhood cancers account for only 2% of neoplasms affecting the general population, they represent the second cause of childhood mortality in industrialized countries, in spite of remarkable advances achieved in survival rates.

According to data from the National Pediatric Cancer Registry, the annual incidence of pediatric cancers in Spain is 132 new cases per million children aged between 0-15 years. HD constitutes 5.5% of all pediatric cancers (3,4).

Definition and Pathology

HD is a malignant tumor characterized by pleomorphic lymphocytic and histiocytic infiltrate with multinucleated Reed-Sternberg cells. Reed-Sternberg cell is a monoclonal and aneuploid cell and can form tumors in immunocompromised animals. Of all the cells present in HD affected tissues, only 2% are RS cells, the remaining cells include lymphocytes, macrophages, granulocytes and eosinophils. Recent studies indicate that RS cells are clones of B origin, which are located in the lymphoid germinal centres. These cells secrete powerful cytokines, which are responsible for B symptoms of the disease, while promoting growth and helping to avoid immunologic vigilance. A RS cell produces at least 12 cytokines, including interleukin-1, interleukin-6 and tumor necrosis factor, and any of which could be responsible for HD systemic symptoms (5,6,7). The malignant RS cells are known to constitutively express high levels of activated nuclear factor kappaB (NFkB), which plays an important role in their survival (8). This aberrant activation of NFkB has been linked to genetic defects in the NFkB inhibitors genes (9), to Epstein-Barr viral infection, and to stimulation by cytokines. HD is divided into four categories: lymphocytic predominance, mixed cellularity, lymphocytic depletion and nodular sclerosis. About two thirds of pediatric patients present with nodular sclerosis subtype at diagnosis. Patients with lymphocytic predominant subtype generally have localized disease and are asymptomatic. Nowadays, with multiagent chemotherapy regimens, histologic subtypes have no influence on the disease outcome.

Differential diagnosis

HD must be differentiated from other causes of lymphadenopathy. The differential diagnosis of adenopathy may include inflammatory causes such as atypical mycobacterial infections, cat-scratch disease and infectious mononucleosis as well as other primary or metastatic tumors. Non-Hodgkin's Lymphoma should be included in differential diagnosis because it may present with signs and symptoms similar to those of HD.

Clinical presentation

The primary nodal site of HD is situated above the diaphragm in two-thirds of patients. The usual clinical presentation consists of painless cervical or supraclavicular adenopathy. If HD arises within the chest (mediastinal involvement), there may be no symptoms or

signs until compression of the airway causes respiratory distress. Splenomegaly and hepatomegaly often indicate advanced disease. The systemic symptoms of fever, weight loss of 10% and night sweats are well known as B symptoms (10).

Diagnostic methods

Clinical examination is important for the detection of peripheral node involvement. The chest radiological evaluation by conventional radiology and CT scan must be performed. CT scan localised on neck should be performed in cervical node enlargement. CT scan and MRI both provide useful information about infradiaphragmatic disease. Gallium scan is a useful diagnostic method in Hodgkin's disease. Positron emission tomography is a new diagnostic method that is currently under investigation. Bone marrow involvement at diagnosis is not usual. Finally, excisional lymph node biopsy is a better biopsy approach for histological diagnosis.

Management including treatment

Currently, more than 90% of children diagnosed with HD benefit from complete remission and prolonged disease-free survival. For years, the treatment of HD children has been based on the same therapeutic concept as that applied to adults, *i.e.* laparotomy for staging and possible splenectomy, which causes high morbidity, and treatment with standard doses of radiotherapy (3600 - 4000 cGy) applied as mantle field (neck, chest and axilla) or standard inverted-Y field (abdominal para-aortic and spleen field). This type of radiation therapy caused cosmetic anomalies and unacceptable skeletal abnormalities in children, as well as cardiomyopathy and risk of second tumors, especially thyroid and breasts neoplasias. Multiagent chemotherapy regimens, which appeared in 1964 (MOPP) and 1974 (ABVD) provided a combined therapy directed towards maintaining an elevated rate of survival and a decrease in morbidity in children. Donaldson's study in Stanford was one of the first to demonstrate that combined modality treatment with MOPP and low irradiation doses in the affected field was highly efficacious and was associated with a decreased incidence of late effects (11). Combined modality therapy coupled with progressive advances in new diagnostic methods (CT scan, MR, and Gallium scan) helps to avoid surgical staging and splenectomy. At present, almost all children receive combined chemotherapy with low dose irradiation (1500 - 2000 cGy) solely in the initially involved area. Several studies are now exploring the possibility of avoiding radiotherapy treatment on the basis of the response to chemotherapy regimens. Novel anticancer treatments are being designed

to target specific molecular pathways that are critical for cancer cell growth and survival in lymphoma such as HD (12).

The proteasome inhibitor PS-341 has been recently shown to modulate tumor cell proliferation and survival by inhibiting NFκB and modulating critical cellular regulatory proteins. The *in vitro* activity of PS-341 against HD-derived cell lines suggests that PS-341 may have a therapeutic value for the treatment of HD (13).

The leukocyte activation marker CD30, which is highly expressed on the RS cells is a target for monoclonal antibody (mAb)-based therapies of Hodgkin's disease. Anti-CD30 antibodies have been recently evaluated in phase I studies in patients with relapsed HD or anaplastic large cell lymphoma. These studies demonstrated that anti-CD30 antibody is a promising treatment strategy (14, 15).

Treatment of relapses

Relapse is a serious issue. Patients relapsing after radiotherapy alone can be salvaged with chemotherapy or combined-modality therapy. For these patients, high doses of chemotherapy followed by hematopoietic stem cell transplantation (HSTC) has been investigated with encouraging results when the procedure is carried out in the second complete remission (16). The same approach is performed in refractory HD.

Late effects

The quality of life during and after treatment is a most important issue. Survivors of HD present an elevated risk of conduct disorders (17). Delayed effects of HD treatment in survivors are sterility caused by testicular toxicity of alkylating agents. Cryopreservation of semen has so far received scant attention (18). Sperm storage is complicated by the fact that many HD patients have low sperm counts at presentation.

It is recommended that patients over 10 years of age undergo sexual development evaluation to assess the cryopreservation of semen. Recently, new experimental approaches have been developed to combat male infertility. One of them is an intracytoplasmic injection of sperm cell into the ovocyte. By means of this technique effective fecundation can be achieved even with low quality sperm. The cryopreservation of testicular or ovarian tissue are techniques currently under development.

Prevention from developing cardiomyopathy is based on the use of combined chemotherapy schedules, which enables administration of lower doses of radiotherapy in the mediastinum, or even complete avoidance of radiotherapy. Cardiomyopathy could also be prevented with the development of chemotherapy regimens

using no anthracycline or lower accumulative doses of anthracycline.

Second tumors such as acute myeloid leukemia (AML) or non-Hodgkin Lymphoma are associated with the use of alkylating agents. The median time for development of myelodysplasia and leukemia is approximately 4 years. Solid tumors such as sarcomas or breast carcinomas are associated with radiation therapy. The risk of epithelial neoplasia such as breast cancer is maintained until more than 25 years after treatment. Breast cancer (19) is the second solid neoplasia most frequently found in radiated girls. The risk is related to age (older than 10 years) at the time of radiation and to the radiation dose administered. It seems therefore reasonable for women who have had mantle-type radiotherapy to undergo an early breast examination.

Chemotherapy regimens are being studied to limit the use of alkylating agents and anthracycline in order to lower the risks of second neoplasias, loss of fertility and cardiomyopathy. While developing future treatments for HD, efficacy and potential associated risks must be taken into account. Curative treatment associated with minimal morbidity and an highest quality of life should be achieved.

Children with cancer should be referred to multidisciplinary team in pediatric oncology units with experience in treating pediatric cancers.

Etiology

Epstein-Barr virus (EBV) has been implicated in the etiology of HD. Indirect evidence, based on epidemiologic data relating to bimodal distribution patterns, suggests that delayed exposure to a common infection is an etiopathologic mechanism in HD. Serologic data, such as elevated levels of specific antibodies in HD patients, or the risk of HD following mononucleosis infection support also this hypothesis. It has not been determined whether the serologic data reflect the pathogenic role of the virus or, on the contrary, the consequence of an immune defect following the reactivation of the infection by Epstein-Barr virus (20,21,22).

The presence in the tumor tissue of EBV DNA and of RNA virus in RS cells has subsequently provided direct evidence for the association of HD and EBV. In cases of positive EBV, the infection of RS cells occurs prior to clonal expansion and it seems that the virus is necessary for the maintenance and progression of the disease. A higher incidence of association HD/ EBV is found in underdeveloped countries in males, in pediatric patients under 10 years of age as well as in mixed cellularity type. EBV is probably a pathologic agent in a HD subgroup, although it is not a necessary factor for the development of HD. Other studies suggest genetic susceptibility to HD and risk factors such

as exposure to pesticides or tonsillectomy, confirming the hypothesis of multiple etiology (23). However, the different epidemiological studies supporting the existence of multiple risk factors require a profound methodological validation of their results.

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