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EARLY CLINICAL MANIFESTATIONS IN HODGKIN'S LYMPHOMA

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Hodgkin's lymphoma, clinically described by Thomas Hodgkin in 1832, is a neoplastic disease of the lymph nodes. The paper presents the results of a study of early clinical manifestations in classical Hodgkin's lymphoma (the incidence of signs and symptoms at the date of presentation of the patient to the physician for confirmation of diagnosis) and the evaluation of the therapeutic results and prognosis of Hodgkin's disease in relation to the anatomical-clinical-biological stage. The research was performed on a group of 91 subjects followed in the Hematology Clinic of «Fundeni» Clinical Institute/Hospital, Bucharest, during 1999-2009. Patients' age varied between 15 and 75 years. The diagnosis of Hodgkin's lymphoma was based on the histopathological examination of the disease (Rye classification, 1966). For the most accurate inventory of disease determinations, for some patients have it has been resorted to staging the abdominal extension of lesions thru large laparotomy with splenectomy, liver biopsy puncture, and abdominal ganglion biopsy, adopting the proposed staging classification proposed at Ann Arbor in 1971. All stages were subdivided into A-Type (no general signs) and B-Type (with the presence of general signs). At the time of the study, only 69 patients out of 91 could be evaluated, 14 being lost from evidence and 8 recording discontinuous treatment. Male predominance was observed. Most of the patients were diagnosed in stage II and III of the disease. The prognosis of Hodgkin's lymphoma is related to the clinical stage in which the patient is diagnosed. The prognosis of Hodgkin's disease depends on the clinical stage in which the patient is diagnosed.

Keywords: Hodgkin's lymphoma, early clinical manifestations, prognosis.

INTRODUCTION

Hodgkin's lymphoma (also known as Hodgkin's disease, malignant lympho-granulomatosis) was clinically described by Thomas Hodgkin in 1832[1] and referred to as Hodgkin's disease by Samuel Wilks in 1866[2]. It is a relatively rare condition in the general population, with an annual incidence in Europe of 2.2 per 100,000 inhabitants.

The etiology of Hodgkin's lymphoma is unknown. Many of the morphological aspects and clinical manifestations of the disease suggest the existence of an inflammatory factor in the production of the disease, which has incited many authors from the end of the last century to involve an infectious agent in the etiology of the disease. Koch bacillus, diphtheroids, corynebacterium, Brucella were incriminated. All of these hypotheses were refuted. Today, the malignant nature of the disease is recognized and proved unanimously[3–6]. Genetic predisposition also plays an important role in the pathogenesis of the disease with studies showing that 1% of cases have a family history of the disease. Recent research has shown in Hodgkin's lymphoma patients a prevalence of the 4C antigens of the HLA System (HLA-B8)[7,8].

Primary involvement of the cervical, mediastinal or intestinal lymph nodes has led some researchers to support the idea of an infectious agent with a digestive and / or respiratory entry[6, 9]. Current research is directed at herpes viruses (Epstein-Barr virus). Studies show that approximately 30% of cases of Hodgkin's lymphoma are positive for Epstein-Barr virus proteins and an increased incidence of Hodgkin's lymphoma after infection with this virus (1 out of 1,000 cases)[10]. However, the mechanism by which EBV infection determines the occurrence of Hodgkin's lymphoma is not known.

Two main processes are involved in the occurrence of Hodgkin's lymphoma: malignant

transformation and immune tissue reaction to neoplastic transformed cells. Neoplastic cells are represented by Sternberg-Reed cells and Hodgkin's cells. For some authors, they are transformed lymphocytes, while for others, based on cytochrometic data and three-dimensional electron microscopy, they come from transformed macrophages[11, 12]. In the early 1980s, the first specific antigen (CD30) was identified on the surface of Sternberg-Reed and Hodgkin cells, and then CD20 antigen (specific to B-lymphocytes) in some of them. Since the 1990s, with the development of polymerase chain reaction (PCR) techniques and the necessary primers (for heavy and light chains of immunoglobulins but also for the T lymphocyte receptor) and also the technique that allowed the isolation of single Reed-Sternberg cells thru tissue microdissection, the clonal origin of their pre-apoptotic B lymphocyte was establish. From a clinical point of view, Hodgkin's lymphoma has 4 evolutionary stages: I, II, III and IV. Symptomology of the disease is dominated, on the one hand, by the increase in lymphoid organ volume and, on the other hand, by the presence of general disorders.

The positive diagnosis is determined only morphologically, based on the biopsy exam.

From the histological point of view, classical Hodgkin's lymphoma is classified into 4 types: LR (lymphocyte-rich), NS (nodular sclerosis), MC (mixed cellularity) and LD (lymphocyte-depleted).

MATERIAL AND METHODS

The research was performed on a group of 91 subjects followed in the Hematology Clinic of "Fundeni" Clinical Institute/Hospital, Bucharest, 1999–2009, so that sufficient time was allowed for evaluating the therapeutic outcomes and the prognosis of the disease in correlation with the anatomical-clinical-biological stage and the histological type.

Patients' age varied between 15 and 75 years and the diagnosis of Hodgkin's disease was based on the histopathological examination, using the classification with the highest accessibility and practical applicability proposed by Lukes and Butler (Rye, 1966) which, however, has some flaws: not always the involvement of an extralymphatic organ has the evolution and prognostic value of a stage IV (*e.g.*, single primary sites of involvement, or parenchymal extension by contiguity from a nearby ganglion, which respond to therapy and are actually curable just as the disease confined to lymph nodes). It has also been shown[6,13] that splenic involvement has another prognostic significance than that of ganglia; it precedes and predicts hepatic involvement. For the clinical staging of Hodgkin's lymphoma, we used Ann Arbor staging system (1971), which comprises[6,13]:

Stage I: only 1 lymph node area or lymphoid organ (I) is involved or the cancer is found only in 1 part of 1 organ outside the lymph system (I_E).

Stage II: Two or more lymph node regions on the same side of the diaphragm are involved (II) and/or localized involvement of a single extralymphatic organ/site on the same side of the diaphragm (II_E);

Stage III: lymph node regions on both sides of the diaphragm are involved (III), including localized involvement of a single extralymphatic organ/site (III_E) or spleen involvement (III_S) or involvement of the spleen plus lymph node(s) above the diaphragm/both (III_{ES});

Stage IV: diffuse or disseminated (multifocal) involvement of one or more extralymphatic organ(s)/site(s) (liver, bone marrow, lungs) with or without associated enlarged lymph nodes.

All stages were subdivided into A-Type (no general signs) and B-Type (with general signs: unexplained fever greater than 38°C, unintentional weight loss of >10% of normal body weight over a period of 6 months or less, night sweats, generalized pruritus).

It was considered a complete remission the return to normal of all enlarged lymphoid organs, in parallel with the disappearance of the general phenomena and no evidence of active disease as indicated by imaging tests such as CT, PET, and sometimes bone marrow biopsy. Partial remission was considered an incomplete treatment response, with more than 50% reduction in the initial tumor volume and disappearance of general phenomena, restoration to normal of biological samples or the absence of tumor involvement, but with the persistence of abnormal biological test results (VSH, fibrinogen). Therapeutic failures were considered the cases that did not show any remission.

RESULTS AND DISCUSSIONS

Within our study sample (N=91 patients), analyzing the incidence of the disease by age, we observed a higher frequency between 25–34 years, after which it decreases in the following decades (Table 1).

Considering the distribution of all 91 cases by sex, a predominance of male sex was observed (56.06% vs. 43.95%) (Table 1).

Table 1

The incidence of Hodgkin's lymphoma according to age and sex in the studied group

Age (years)	15–24	25–34	35–44	45–54	55–64	65–74	Total
Males %	13.18	9.89	13.18	6.59	5.49	7.69	56.04
Females %	10.98	15.38	5.49	2.19	5.49	4.39	43.96
Number of cases %	24.17	25.27	18.68	8.79	10.98	12.08	100

Table 2

The incidence of signs and symptoms (early clinical manifestation) at the time of clinical diagnosis

Signs and symptoms		Number of cases	%
lymphadenopathy		15	16.48
lymphadenopathy + general signs	Fever	57	62.63
	Weight loss	56	61.53
	Sweats	34	37.36
	Pruritus	14	15.38
lymphadenopathy + functional signs (symptoms)	Dyspnoea	11	12.08
	Cough	6	6.59
	Edem limb	3	3.29
	Dysphagia	2	2.19
Functional signs		1	1.09

Table 3

The incidence of Hodgkin lymphoma localizations at the time of clinical diagnosis

Hodgkin lymphoma localization			Number of cases	%
Peripheral lymphadenopathy	**Laterocervical**	Unilateral	20	21.97
		Bilateral	36	39.56
	Axillary	Unilateral	17	18.68
		Bilateral	34	37.36
	Supraclavicular	Unilateral	16	17.58
		Bilateral	31	34.06
	Submandibular	Unilateral	5	5.49
		Bilateral	21	23.07
	Ilio-inguinal	Unilateral	7	7.69
		Bilateral	18	19.78
Internal adenopathy	**Ilio-mediastinal**		14	15.38
	Retroperitoneal		12	13.18
Splenomegaly			19	20,87
Hepatomegaly			33	36.26

Table 4

The incidence of unilateral localizations of peripheral lymphadenopathies in early clinical manifestations of Hodgkin's lymphoma

	Peripheral lymphadenopathies				
Hemibody	Laterocervical	Supraclavicular	Axillary	Submandibular	Ilio-inguinal
Right	40%	12.5%	29.42%	100%	14.29%
Left	60%	87.5%	70.58%	0	85.7%

Regarding the incidence of signs and symptoms (early clinical manifestations) at the date of first presentation to doctor for diagnosis confirmation (Table 2), the most common sign was lymphadenopathy (97.8%) associated with fever (63%) and the weight loss (61.53%).

Lymphadenopathy as a single sign of Hodgkin's lymphoma occurred in 15 patients (16.48% of cases), in other 74 cases (81.32%) being associated with general and / or functional signs.

Pruritus was present in 15.38% of cases associated with lymphadenopathy or other general signs.

The weight loss of more than 10% of the patient's initial body weight in the last 6 months before diagnosis was found in 56 cases (61.53%), associated with other signs and symptoms of HL.

Of the functional signs, dyspnea was present in 12.08% of cases, being associated in 2 cases with dry cough.

Two patients presented a poor symptomatology (subfebrility and weight loss), without clinically detectable adenopathies, for which many paraclinical and laboratory investigations were performed and finally exploratory laparotomy for a clear diagnosis and correct staging.

The incidence of clinically detectable localizations at the time of diagnosis in the 91 investigated subjects was extensively studied and 89 patients (97.8%) had lymphadenopathy, 19 (20.87%) splenomegaly and 33 (36.26%) hepatomegaly (Table 3).

Regarding lymphadenopathy, the most frequent localization was cervical (61.53% of cases), followed by axillary (56.04%) and supraclavicular (51.65%). Most often, cervical adenopathy was associated with other lymphadenopathies (axillary, supraclavicular, submental, inguinal, retroperitoneal, and ilio-mediastinal). The least common were ilio-mediastinal (15.38%) and retroperitoneal (13.18%) lymphade-nopathies.

Abdominal lymphadenopathy has been associated with other supradiaphragmatic peripheral adenopathy in 12 cases and with the mediastinal one in 2 cases.

The study found that predominantly the lymph nodes in the left half of the body were affected (Table 4).

During the patients' follow-up period, laboratory investigations have provided valuable insights, assessing the evolutionary and active phase of the disease, or the phase of remission and the immune status of the patients.

VSH and fibrinogen were found initially elevated in 62 subjects indicating the active phase of the disease.

The number of white blood cells was increased in 24 cases and in 17 cases there was a decrease in the absolute number of peripheral lymphocytes.

Imaging investigations – chest x-ray, abdominal and soft tissue ultrasound scans – might signal a problem/constitute a warning sign or objectify clinical examination when they are positive, but have low sensitivity.

The useful diagnostic investigation is the computed tomography (CT) scan of the cervical, thoracic, abdominal and pelvic regions (without contrast material, except in well-defined situations), which highlights particularly the profound lymphadenopathies and extranodal involvement, as well as their size and orientation – information that guide the surgical approach during histopathological examination procedures when there are no peripheral adenopathies.

The paraclinical investigations used for the clinical staging of the disease proved to be very useful (Table 5).

The radiographic examination of the chest was performed on 88 of the 91 patients.

The ultrasound scan was used for abdomen examination in 69 cases (57 with normal appearance, 12 with suspected adenopathy), while computerized axial tomography was performed in 79 cases (67 with normal appearance, 12 with a positive result).

Other paraclinical and laboratory investigations carried out for clinical staging were: bone biopsy puncture in 62 cases (56 normal, 6 positive results), liver biopsy puncture in 4 cases (3 positive results) and bone marrow aspiration in 23 cases (17 normal, 6 positive results).

After all these investigations, the clinical stage of the disease was established: 15 patients were Stage I, 41 Stage II, 30 Stage III, and 5 Stage IV.

Taking into account the presence of the general signs, no patient in stage I was classified as B-type, while in stage II their number was considerable (31 with general signs versus 10 without general signs); in stages III and IV all patients had general signs (Table 6).

The initial treatment of the 89 patients (of 91 diagnosed patients, 2 refused treatment) was different, depending on their clinical status and histological type: 49 cases received chemotherapy; in 36 cases chemotherapy was associated with radiotherapy (cobalt therapy) and in 3 cases chemotherapy was associated with splenectomy.

Table 5

Paraclinical methods used in staging

Method	Number of cases	Normal result	Positive result
Chest radiography	88	74	14
Ultrasound	69	57	12
Computed axial tomography	79	67	12
Bone marrow biopsy puncture	62	56	6
Hepatic biopsy puncture	4	1	3
Bone marrow aspiration	23	17	6

Table 6

Distribution of sample patients, by clinical stage

Clinical stage	I		II		III		IV		Total
Type	A	B	A	B	A	B	A	B	
Number of cases	15	-	10	31	-	30	-	5	91
Total	15		41		30		5		91
%	16.48		45.05		32.96		5.49		100

Treatment results were relatively good: 37 of them had partial remission (40.66%), 22 had total remission (24.17%), and 32 failed treatment (35.17%). Analyzing the therapeutic outcomes by the clinical stage at diagnosis, it was noted that of the 22 patients in complete remission 11 were in stage I (50%), 9 in stage II (40.9%) and 2 (9.1%) in stage III. Of the patients with partial remission (37 cases), 2 were in stage I (5.04%), 21 in stage II (56.75%), 11 in stage III (29.72%) and 3 in stage IV (8.49%). The therapeutic failure was recorded in 32 cases, of which 2 in stage I (6.25%), 11 in stage II (34.37%), 17 in stage III (53.12%) and 2 in stage IV (6.26%).

Of the 91 patients, only 69 could be considered as evaluable, because 8 had treatment discontinuations and 14 were lost from records after 12 months of treatment. Of the patients with uninterrupted treatment and those who had entered remission, in 36 cases the relapse occurred (in 4 cases the recurrence was only biological, with no clinically detectable localizations). Of the 36 cases of relapses, 22 were male.

CONCLUSIONS

The analysis of the results obtained by studying 91 patients (a relatively small sample, but is a relatively rare condition in the general population) led to the following conclusions:

1. Male predominance was observed;
2. The disease is most commonly encountered between 35-54 years;
3. Lymphadenopathy, with or without general and/or functional signs, was – at the time of diagnosis – the most frequent of the early clinical manifestations of classical Hodgkin's lymphoma;
4. The most commonly involved lymph nodes were in the left hemibody;
5. The most affected lymph node group was the cervical one, followed by the axillary and supraclavicular groups.
6. The majority of patients were diagnosed in stages II and III of the disease; starting with the second stage, the Type-B of the disease had an increasing share;
7. The therapeutic outcomes depend on the results of pre-therapeutic evaluation of the disease;
8. The highest recurrence rate was recorded in stage III patients (53%) followed by stage II patients (34%);
9. The highest number of complete remissions was recorded in stage I patients, (50%) followed by stage II patients (40.9%);
10. The initial treatment (poly-chemotherapy and/or radiotherapy) associated or not with splenectomy, as well as the treatment of relapses, conducted according to the diagnosed stage, have led to an improvement in the survival rate of the patients, the highest survival rate being recorded in stage II patients (51%).

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