Introduction

Hodgkin's lymphoma represents the most common subtype of malignant lymphoma in young people in the Western world. Regarding all population it accounts for approximately11% of all malignant lymphomas ***(Horning S et al., 2008).***

HL is one of the most curable malignancies today. After a minimum follow-up of 5 years, more than 90% of patients are still alive and 80% are considered cured. These rewarding results have been obtained by; (i) increasing accuracy of staging procedures; (ii) the different treatment strategies tailored to well-defined categories of patients with different risks of treatment failure; (iii) the peculiar neoplastic tissue architecture in HL and (iv) the marked chemosensitivity and radiosensitivity of the tumor ***(Jemal A et al., 2009)***.

The management of HL has been steadily improved by the increasingly accurate imaging techniques; positron emission tomography or PET/computed tomography. Currently PET is widely utilized for response assessment after completion of therapy and pretreatment staging and assessment of response during therapy and therapy monitoring. In pretreatment staging, PET cannot replace CT or bone marrow biopsy; however, it can provide complementary information to both CT and BMB also blood chemistry as liver and kidney function tests, liver albumin and complete blood picture may help the diagnosis of HL ***(Delbeke D et al., 2009)***.

Recently, combined PET and CT scanners have emerged as a promising imaging modality and are being more routinely applied in clinical situations ***(Tatsumi M et al., 2005).***

However, HL has become a curable malignancy for most patients during the last decades; many controversies still exist on the optimal strategy of how to cure patients. The key question is how to balance the risks and toxicities of chemotherapy and radiotherapy against the need for a definite treatment for early or advanced-stage HL patients ***(Stroobants S et al., 2007).***

In order to achieve a high cure rate while at the same time minimizing acute and late toxicity for patients with HL. Several clinical trials were carried out according to the stage of the disease ***(Pfistner B et al., 2007).***

For limited-stage (I/II) disease; extended- field radiotherapy (EFRT) was the treatment of choice for this stage, but recently with the increasing awareness of serious long-term toxicity after EFRT promoted the development of combined modality treatment approaches. Combined modality has the evident advantage of combining two efficacious treatment modalities so that the extent of both RT, as well as CT, can be reduced in the combined treatment design ***(Connors J et al., 2010).***

Nowadays clinical stage I/II HL patients are generally divided into an early favorable and an early unfavorable subgroups based on; 1- the extent of disease, 2- the age of the patient, 3- the number of involved nodes, 4-the erythrocyte

sedimentation rate, 5-the presence of B symptoms and 6-the size of mediastinal bulk ***(Yeddes I et al., 2010)***.

Treatment of early favorable and early unfavorable HL have been investigated in several clinical trials carried out by the[European Organization for Research and Treatment of Cancer] EORTC/GELA (Groupe d'Etude des Lymphomes de l'Adulte) and the German Hodgkin Study Group (GHSG). These trials proved that two cycles of adriamycin, bleomycin, vinblastine, dacarbazine (ABVD) followed by 20 Gy involved field irradiation therapy IFRT are the new standard treatment for early favorable HL patients ***(Franklin J et al., 2007).***

Also they proved that the combined modality treatment with four cycles of ABVD, followed by IFRT, is the preferred treatment approach for patients with unfavorable early stage I/II disease ***(Rigacci L et al., 2010)***.

For advanced stage HL (stage III or IV or any stage with bulky disease or B symptoms);- over the past years, new regimens have been developed for these patients based on the premise of either improved efficacy or reduced toxicity. Dose-escalated bleomycin, etoposide, doxorubicin (Adriamycin), cyclophospha-mide, vincristine (Oncovin), procarbazine, and prednisone (escalated BEACOPP or escB) has emerged as a very effective regimen and yielded significantly better survival compared with other modified versions BEACOPP through several clinical trials ***(Johnson P et al., 2005).***

But escB has not been widely adopted because of higher acute hematologic toxicity, estimated 10-year

cumulative incidence of acute myelogenous leukemia/ myelodysplasia (3.2%, 2.2%, and o.4%, respectively) and nearly universal infertility ***(Brillant C et al., 2009).***

Recently, 2 Italian studies compared ABVD with variations of the BEACOPP regimen. The first trial reported that 4 cycles of esc B and 2 cycles of bas B resulted in superior progression free survival (PFS) compared with 6 cycles of ABVD (5-year rates, 81% and 68%, respectively*)* ***(Chisesi T et al., 2007).*** But unfortunately higher rates of acute grade neutropenia and severe infections were reported. The second trial compared 6-8 cycles of ABVD versus 4 cycles of escB followed by 4 cycles of basB as frontline therapy, with preplanned high-dose therapy as salvage for patients with partial response (PR). Results were similar to the first trial with more infections, and no differences in the overall survival (90% vs 91%) ***(Engert A et al., 2010)***.

Another regimen tested as an alternative to ABVD is Stanford V, a combined modality therapy (CMT) approach. The results were reported in the favor of ABVD regimen which is more efficient and less toxic ***(Gordon L et al., 2010)***.

Also several trials were carried out but revealed the same results. So (ABVD) is considered the standard treatment for advanced HL, providing an excellent balance of efficacy and toxicity, but for selected patients, the Stanford V regimen remains a valid option as frontline therapy because of the brief duration of treatment and lower cumulative doses of adriamycin and bleomycin, although long-term follow-up is

required to accurately assess the impact of the modified RT in Stanford V outcome ***(Hoskin P et al., 2009).***

For patients with relapsed or progressive disease targeted therapies with antibody drug conjugates (ADC) and monoclonal antibodies have shown promising results for these patients ***(Viviani S et al., 2010)***.

Although patients' evaluation and staging at diagnosis are important, the management of Hodgkin's lymphoma involves a complex series of algorithms requiring interim and overall response assessment, careful follow-up, repeat assessment, and salvage management of recurrent disease ***(Sureda A et al., 2010)***.

Aim of Work:

The aim of work is to provide an optimum view of the new trends in assessment and management of Hodgkin Lymphoma.

Epidemiology of Hodgkin's Lymphoma

Hodgkin's lymphoma (HL), formerly called Hodgkin's disease, is a malignant tumor of the lymphatic system ***(Schnitzer., 2009).*** It was first recorded by Thomas Hodgkin in 1832, when he described seven patients suffering from enlargement of lymph nodes and spleen as a new disease entity ***(Thomas et al., 2002).***

Incidence

The incidence of Hodgkin's lymphoma shows marked heterogeneity with respect to age, gender, race, geographic area, social class and histological subtype**.** It affects less than 200.000 people in the US population. About 8000 new cases of Hodgkin's lymphoma occur each year in the United States. 1500 people in the US die from Hodgkin's lymphoma each year. The annual incidence of Hodgkin's lymphoma appears stable over the past several decades. HL had a worldwide incidence of 67,887cases in 2008, with an age standardized rate of 1.0 per 100,000 (both genders), HL represents about 23% of lymphomas in Egypt. (***http://globocan.iarc.fr/*)** incidence expressed in ASR (age standardized rate per 100,000) in Egypt is 2, 5.

Age

It has a bimodal age incidence curve in United States, peaking in young adults (aged 15-34 y) and older individuals (>55years***).*** in the United States, Nodular sclerosing (NSHL) subtype predominates in young adults (20s), while Mixed cellularity (MCHL) subtype is more common in children (aged 0-14 ys) ***(Thomas et al., 2002)***. Hodgkin's lymphoma is the third most common cancer in people aged 15-29 years, and the sixth

most commonly diagnosed cancer in children under 14 years ***(Hoffbrand et al., 2011).***

Sex

There is a slight overall male predominance in the incidence of HL 1.3:1, which is most marked in the childhood form. Nodular sclerosing subtype shows a slight female predominance ***(Thomas et al., 2002).***

Risk factors

- The higher the socioeconomic status of person, the greater the risk in the young adult disease.
- It is not possible to conclude that a causal relationship exists between the occupational exposures and risk of Hodgkin's lymphoma.
- Smoking more than 14 cigarettes per day was associated with a 50% increased risk.
- First degree relatives have 5 fold increase risk for HL ***(Rezaei N., 2012).***
- There is a relationship between HL and Epstein-Barr virus (EBV) infection ***(Swerdlow, 2003).*** Patients with a history of infectious mononucleosis due to Epstein-Barr virus may have an increased risk of Hodgkin's lymphoma ***(Alexander et al., 2000).*** Several studies suggest that EBV may be a transforming agent in HL. Patients with a history of EBV infection are at a 2-3 fold higher risk for development of HL. MCHL is more likely to be EBV-associated than NSHL subtype ***(Thomas et al., 2002)***.

- Many studies have found significant increase in risk of HL among patients with AIDS (acquired immune deficiency syndrome) in the developed countries ***(Serraino et al., 2000).*** Patients with HIV (human acquired immune deficiency virus) infection have a 15- fold increase risk to develop HL than the general population ***(Biggar et al., 2006***). They usually present at a more advanced age with associated extranodal involvement and B symptoms ***(Glaser et al., 2003).***

- Also, Human Herpes virus 6 (HHV-6), HHV-7, HHV-8 and cytomegalovirus infections were demonstrated in Hodgkin's lymphoma patients.

Pathology of HL

The World Health Organization (WHO) classification divides HL into 2 main types:

- Lymphocyte- predominant Hodgkin lymphoma (LPHL) accounts for 5% of all HL cases and

- Classical Hodgkin lymphoma (cHL) accounts for 95%. cHL is divided into 4 subtypes:

- Nodular sclerosis cHL (NScHL) -most common histological type in European countries, accounting for 40–70% of cases-,

- Mixed cellularity cHL (MCcHL) account for about 30%,

- Lymphocyte-depleted cHL (LDcHL) account for about less than 5% and

- Lymphocyte-rich cHL (LRcHL) account for about 10% ***(Swerdlow et al., 2008).***

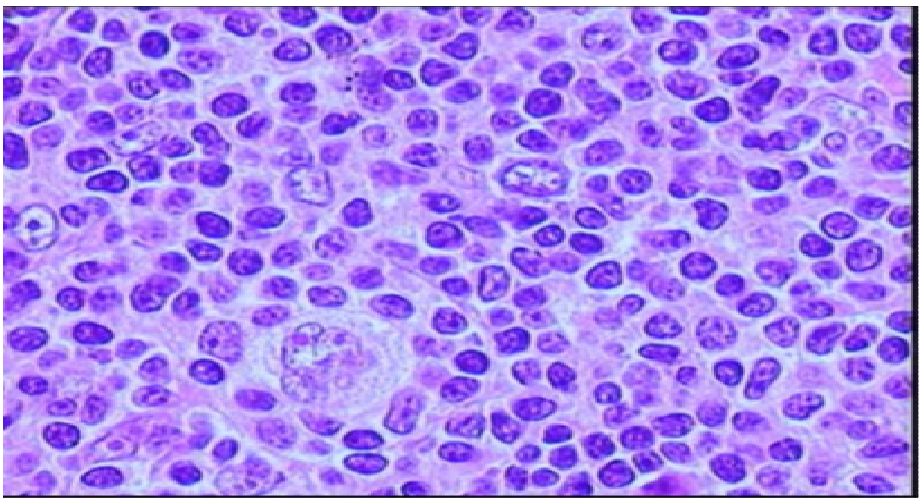
- Histologically, cHL is characterized by a minority of neoplastic cells (1-2%) named H/RS cells (Reed-Stemberg)-

binucleated derived from monoclonal population of B cells-embedded in a rich background of a variety of reactive, mixed inflammatory cells consisting of lymphocytes, plasma cells, neutrophils, eosinophils, and histiocytes ***(Figure 1).***

Whereas LPHL lacks Reed-Stemberg cells but is characterized by the presence of lymphocyte predominant cells, sometimes termed popcorn cells. LPHL can have a nodular or diffuse pattern. The nodular subtype has lymphocyte predominant cells embedded in a background predominantly composed of B lymphocytes, whereas the diffuse subtype has a background consisting mainly of T-cells. ***(Kuppers et al., 2003***).

Concerning the phenotypic findings, expression of the CD30 (Cluster Of differentiation) molecule by H/RS cells is seen in more than 98% of cHLs ***(Bartlet T, 2010).***

CD15, characteristic but not specific for HRS, is detected in about 80% of cHL patients ***(Foyil & Bartlett., 2010).*** H/RS cells usually lack CD45**,** whereas B and, to lesser extent, T cell markers are seen in a proportion of cases. In particular, CD20 is found in 30%–40% of cHL cases (usually EBV negative) and CD79a is found even less often.



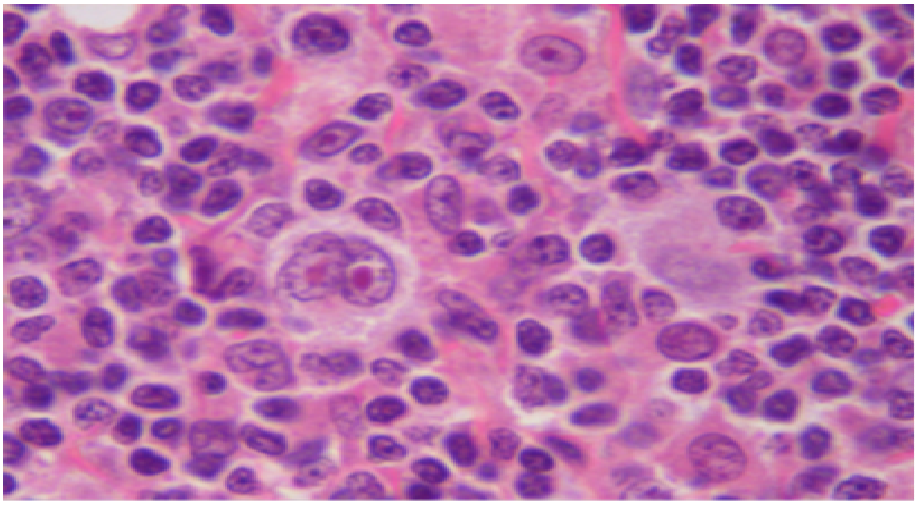


Fig. (1): Re ed-Sternberg cell seen in a cellular background rich in lymphocytes of a classical Hodgkin lymphomaPopcorn cell with typically lobated nuclei seen in a Nodular lymphocyte predominant Hodgkin lymphoma.

Staging

Staging is the most important factor in the initial approach for prognosis and treatment of HL, being the Ann Arbor system with Cotswolds modifications the current staging system used for patients with HL ***(Diehl et al., 2004).***

Stage I Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer's ring) or involvement of a single extra lymphatic site or organ (IE).

Stage II Involvement of two or more lymph node regions on the same side of the diaphragm (hailer nodes, when involved on both sides, constitute stage II disease); localized contiguous involvement of only one extra nodal organ or site and lymph node region(s) on the same side of the diaphragm (IIE). The number of anatomic regions involved should be indicated by a subscript (e.g., II_3).

Stage III Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by involvement of the spleen (III_S) or by localized contiguous involvement of only one extra nodal organ site (IIIE) or both (III SE).

This may be subdivided into stage III-1 or III-2:

Stage III-1 With or without involvement of splenic, hailer, celiac, or portal nodes.

Stage III-2 With involvement of para-aortic, iliac, and mesenteric nodes.

Stage IV Diffuse or disseminated involvement of one or more extranodal organs or tissues, with or without associated lymph node involvement**.**

Lymph node groups: Waldeyer's ring; occipital/ cervical / preauricular/ supraclavicular; infraclavicular; axillary; epitrochlear; mediastinal;right and left hilar (separate); paraaortic; splenic; mesenteric;iliac; inguinal/femoral; popliteal.

Designations applicable to any disease stage

A	No symptoms
B	Fever (temperature, >38°C), drenching night sweats, unexplained loss of >10% body weight within the preceding 6 months.
X	Bulky disease (a widening of the mediastinum by more than one-third or the presence of a nodal mass with a maximal dimension >10 cm).
E	Involvement of a single extranodal site that is contiguous or proximal to the known nodal site.

30% of the patients present with B symptoms overall but only 15-20% of stage I-II have B symptoms.

Patients with HL are usually classified into 3 groups:

1) Early stage favorable (stageI-II with no unfavorable factors)
2) Early stage unfavorable (stageI-II with any unfavorable factor such as large mediastinal adenopathy, significaly elevated ESR, B symptoms, numerous sites of the disease)
3) Advanced stage disease (stageIII-IV).

Unfavorable disease according to NCCN 2013 guidelines is

1- Large mediastinal adenopathy which on chest radiograph measured using the mediastinal mass ratio (MMR) which is the ratio of the maximum diameter of the mass to the maximum intrathoracic diameter;

2- Bulky disease lager than 10 cm, any mass with MMR greater than 0.33 is also defined as bulky disease according to the Cotsworld modification of the Ann Arbor staging system, bulky disease is defined as a mediastinal mass exceeding one third of the internal transverse diameter of the thorax at the T5-T6 interspace on a posteroanterior chest radiograph-another definition of bulk is any single node or nodal mass that is 10 cm or greater in diameter-;

3- Presence of B symptoms,

4- ESR more than 50 mm/h,

5- Disease with four or more regions of involvement ***(Chetaille et al., 2011***).

Also EORTC (European Organization for the Research and Treatment of Cancer) defined unfavorable disease as follow: age 50 or older; large mediastinal adenopathy; with an ESR of more

than 50/h and B symptoms (or with an ESR of more than 30 mm/h in those who have B symptoms); and disease with four or more regions of involvement and by the GHSG (German Hodgkin Study Group) as three or more sites of disease; extranodal extension; mediastinal mass measuring one-third the maximum thoracic diameter or greater; and ESR more than 50 mm/h (more than 30 mm/h if B symptoms present) and by the NCI-C (National Cancer Institute of Canada) as age 40 or older; ESR more than 50 mm/h; and disease with four or more regions of involvement ***(Rezzia N, 2012).***

Prognostic factors

The outcome in cHL patients has been predicted using standard clinical variables such as bulky disease, patient age, number of nodal sites and erythrocyte sedimentation rate. The most widely used and reproducible prognostic score is based on clinical and analytical parameters that make up the International Prognostic Score (IPS). This consists of seven prognostic factors, each of which reduced survival rates by 7% to 8% per year, these factors are:

- Age 45 years or older
- Male gender
- Stage IV disease
- Albumin level below 4 g/dL
- Hemoglobin level below 10.5 g/dL
- Leucocytosis (white blood cell count more than 15,000/mm^3)
- Lymphocytopenia (lymphocyte count less than 8% of the white blood count and/or lymphocyte count less than 600/mm^3

The International Prognostic Score (IPS) is defined by the number of adverse prognostic factors present at diagnosis and each factor represented by one point for a total score ranging from zero to seven. IPS helps to determine clinical management and predict prognosis for patients with stage III-IV disease ***(Cheson BD, 2007).***

In addition to the IPS, number of biological markers has been recognized recently as clinical prognostic factors (including those of the IPS) will further improve the understanding of the disease and the management of patients these factors include surface receptors, intracellular proteins, cytokines, and genetic abnormalities, or alterations in miRNA in HRS cells and surrounding inflammatory cells ***(Bertucci et al., 2011).***

Diagnosis

Signs and Symptoms of lymphoma:

The first sign of lymphoma is a painless lymphadenopathy which involves any of the superficial lymph node in the neck, axilla, inguinal lymph nodes or tissues elsewhere in the body may also as well.80% of the patient present with cervical lymphadeno-pathy, 50% present with mediastinal lymphadenopathy (most likely with NSHL). The spleen, for example, often becomes enlarged in lymphoma which may cause abdominal pain or discomfort.

Also the enlarged lymph node sometimes causes other symptoms by pressing against a vein or lymphatic vessels, a nerve (neurogenic pain, numbness, tingling, nerve root infiltration, meningeal involvement), or the stomach (early feeling of fullness), back pain that suggest massive retroperitoneal lymph node involvement, bone pain suggest areas of bone destruction or