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Clinical presentation and staging of Hodgkin lymphoma

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ABSTRACT

In the present chapter the authors present a brief overview of the diagnostic methods proposed over time for Hodgkin lymphoma (HL) spread detection, moving from surgical procedures, through standard radiological and functional imaging techniques to the present state of the art for HL staging. The main body of the review will be dedicated to the recently published guidelines for lymphoma staging (including HL) agreed by the experts during the 12th International Congress for Malignant Lymphoma in Lugano. The recommendations of the panel on how to integrate flurodeoxyglucose positron emission tomography (FDG-PET) scan in the armamentarium of staging procedures will be presented and commented, with a special emphasis on the utility of special procedures, such as bone marrow trephine biopsy, which is deemed no longer needed in the PET era. While the HL diagnosis is straightforward in most cases, sometimes HL is a subtle disease, difficult to diagnose for the paucity of symptoms, the absence of physical findings, or for concomitant immunologic disorders: a compete overview of the common and rare patterns of HL clinical presentation will be also offered. The future perspective of PET scan use will be based on a operator-independent, quantitative readings of the scan thanks to a plethora of sophisticated dedicated software, which are now available, able to quantify every voxel captured by the tumor to display the metabolically active tumor volume. Moreover, new tracers are now available able to track the new pathways of cellular metabolism beside glycolysis such as amino acids or purine-analogues or specific oncoproteins; the preliminary, promising results will be reported. Preliminary results from other imaging techniques, such as diffusion-weighted magnetic resonance (DW-MRI) will be also reported.

1. Historic outline

Hodgkin lymphoma (HL) has been considered the archetype of tumor staging, restaging and prognostication. Moreover, a combined treatment integrating the most recent and innovative radiotherapy technique and the most active chemotherapy agents, has been for long a model in Oncology to design new clinical trials in a logic sequence, in search of the best effective treatment. In the early seventies the Ann Arbor staging system [1], and later the Cotswolds revised classification [2], first introduced the concept that disease manifestations and tumor bulk identify distinct categories of patients who have a different prognoses and need specific therapeutic approaches. At that time a surgical approach (the so-called staging laparotomy with splenectomy and multiple nodal and organ biopsies) was first proposed for tumor staging [3]. This procedure had the merit of spurring the knowledge on the physiopathology of disease spread, first introducing the concept the HL disseminates first for contiguity via lymphatic channels and in the later stages of disease, through the circulatory stream. Nonetheless, it proved cumbersome and even burdened by some morbidity; moreover, with the advent of new radiologic diagnostic facilities this invasive approach was surmounted in the beginning of the eighties by lymphography and contrast-enhanced computed tomography (ceCT). The latter, in particular, proved a readily accessible, non-invasive diagnostic tool, with a high sensitivity and overall accuracy for tumor spread detection and it rapidly became the gold standard for tumor staging not only HL, but for all the lymphoma subsets. Moreover, in some of these studies the results of staging laparotomy were used as reference for assessing sensitivity, specificity and overall accuracy of these new radiologic methods [4]. Meanwhile, the growing evidence that the tumor per se and the host reaction

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against the tumor were the main prognostic parameters correlated to tumor survival provided the frame for a new classification of prognostic factors in HL as (a) tumor-related, (b) host-related, and (c) environment- related [5] which were able to identify three different groups of HL patients with different long-term prognosis: the early favorable, early unfavorable and advanced HL [6]. A further big stride toward a better accuracy of staging, restaging, and prognostication in lymphoma has been accomplished in the early 1990s by the widespread use of functional imaging with total-body scintigraphy with gallium 67 first and later with positron emission tomography (PET), using the glucose analogue ^{18}F-fluorodeoxyglucose (FDG). FDG-PET proved able to detect the presence of viable tumor tissue, which turned out very useful in the early and late assessment of HL treatment response.

2. Clinical presentation

HL clinical presentation typically starts with lymph node enlargement, in absence of any subjective symptom or other concomitant clinical signs. Patients seek medical advice because of an enlarged, painless, palpable lymph node, which sometimes shows spontaneous fluctuations of size, more frequently in the upper or lower cervical area (60% of the cases). Other less frequently involved areas are mediastinal (20%), inguinal (7%), axillary (5%) and other (8%). Mediastinal adenopathy could be detected incidentally or, in case of massive lesions (bulky), for persisting dry cough or thoracic discomfort. In rare cases a superior vena cava syndrome is also present, and associated with edema of upper limbs and dyspnoea. Sub-diaphragmatic presentation is rare, and more often observed in the elderly male. HL could virtually involve all nodal and extranodal sites (ENS), the latter in nearly one quarter of the cases [7–10]. The most common ENS is bone or bone marrow, followed by lung, liver, and muscle. Rare extranodal localization in anecdotal reports has been described in the central nervous system [11] and skin [12]. Cutaneous abnormalities, however, are frequently observed as onset manifestation in HL as erythema nodosum [13], psoriasiform or pemphigoid-like manifestation [14], or ichthyosiform dermatitis [15], which could occur as synchronous or metachronous disorders. The most common symptoms include fever, night sweats, weight loss, and pruritus. Fever has been in the past described as intermittent, with periods afebrile interspersed by episodes of fever usually not exceeding 38°C, most evident in the evening, as originally described by Pel and Ebstein [16]. However, hyperpyrexia with spikes up to 40°C and other patterns of fever have been reported, with the conclusion that “the characteristic of HL fever is the lack of characteristics”. Weight loss is defined as a reduction equal or higher than 10% of the patient weight in the last 6 months. Night sweats are not fever-related but are dependent on cytokines, and could be so intense to drench bed sheets and cloths, forcing the patient to change dresses several times in the day. Itching is considered an unspecific symptom of HL; however this could be the only complaint of the patient and, in cases associated with isolated mediastinal enlarged lymph nodes, could be a puzzling diagnostic dilemma, until a standard chest x-ray discloses the diagnosis.

HL is not rarely heralded, months or years before disease onset, by autoimmune disorders such as rheumatoid arthritis, rheumatic heart disease, Crohn’s disease, rheumatic polymyalgia, systemic lupus erythematosus, megaloblastic anaemia, and ankylosing spondylitis. This is a noteworthy association with important clinical consequences as the association of these disorders sensibly worsen the HL prognosis, both in men and women (3-year progression-free survival [PFS] of 48.5% *v* 59.2 and 46.0% *v* 63.3%, respectively) [17]. A number of cases showing atypical HL presentation mimicking myelofibrosis with myeloid metaplasia have been reported, characterized by pancytopenia, liver and spleen enlargement, dry tap at bone marrow aspiration, and B symptoms. Diagnosis of HL could be difficult in these cases and could delayed up to 2 years as Hodgkin and Reed-Sternberg cell are rarely observed in bone marrow trephine biopsy. A biopsy of enlarged lymph nodes or splenectomy usually helps to unravel the diagnosis [18].

HL is rare in infants, it represents $<$ 5 % of cancers occurring in children under 15 years old, but it is the most common cancer in adolescents (approximately 20% of cancers in the age group 15–19 years) [19]. Presenting symptoms and signs of HL in children include enlarged, painless, palpable lymphadenopathy (80%), mediastinal mass (75%), and systemic B symptoms (25%) [20]. Stages IIII constitute up to 89% of pediatric HL patients [21]. Mixed cellularity and nodular lymphocyte-predominant HL are more frequent in younger children $<$15 years old than in adolescents and young adults (approximately 45% and 20% *v* 25% and 8%, respectively). On the other hand, nodular sclerosis, the most frequent (80%) subtype in in adolescents and young adults, represents only 18%–40% in younger children [21,22]. A peculiar disease presentation is also observed in HL affecting the elderly (aged $>$60 years): mixed cellularity is the prominent histologic sub-type (up to 50%) [23], and Epstein-Barr virus infection is correlated to the disease in up to 50% of the cases: both factors adversely affect disease outcome [24]. Clinically, older patients present with advanced disease, frequently with infra-diaphragmatic nodal disease and B symptoms, but less commonly with a bulky mediastinal mass [25,26]. Moreover comorbidities and poor performance status are also associated. Altogether, these disease characteristics increase treatment related morbidity and mortality [25,26], even if frailty ad co-morbidity are independent from these peculiar disease manifestations in the elderly. A comprehensive geriatric assessment is recommended to properly and independently evaluate comorbid conditions and performance status before therapy onset [27]. The peak incidence of HL coincides with female reproductive age. In fact, HL is one of the most common lymphomas diagnosed during pregnancy [28]. Therefore pregnancy testing should be included in baseline laboratory workup [29]. Similar to non-pregnant patients HL presents with an enlarged, painless, palpable lymph node or mediastinal syndrome [28,29]. B symptoms were variably documented in retrospective series from totally absent to a frequently presenting feature at diagnosis [30]. Importantly, the stage breakdown at diagnosis was similar to non-pregnant patients, as stage I represents 25%; stage II 46%; stage III 17%; and stage IV 12% of the patients [31,32]. Staging is performed with chest x-ray with adequate abdominal shielding and magnetic resonance imaging (MRI) or ultrasound (US) of the abdomen [33], as CeCT and FDG-PET are contraindicated [34,35]. If the patient is in the third trimester and treatment initiation is deferred until delivery, staging should also be performed after delivery [29,31].

3. Staging

International recommendations for staging and response assessment of malignant lymphoma—the Lugano Classification—were recently published along with revised recommendations for the use of imaging in lymphoma [36,37]. These consensus papers recommend the routine use of FDG-PET/computed tomography (CT) for staging of HL, which is FDG-avid almost without exception.

The purpose of staging is to assess the extent and burden of disease, which is crucial for the choice of treatment strategy and for the assessment of prognosis. On the basis of staging, the