CASE REPORT

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Relationship between classical Hodgkin's lymphoma and diffuse large B-cell lymphoma: Separate entity or biologic continuum

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ABSTRACT

Introduction: Cases of patients with non-Hodgkin's lymphoma observed after therapy for Hodgkin lymphoma have been reported. However, occurrence of non-Hodgkin's lymphomas in such settings at a previously uninvolved site is extremely rare. The mechanism behind this remains obscure thereby presenting diagnostic and therapeutic dilemma for the treating physician. **Case Report:** We report a case of a 62-year-old woman who developed a large B-cell non-Hodgkin's lymphoma at a different anatomic site six months after receiving high dose chemotherapy and autologous stem cell transplantation for her relapsed Hodgkin lymphoma. We treated her with conventional combination chemoimmunotherapy following which she achieved durable complete remission. **Conclusion:** This case highlights the intriguing relationship between classical Hodgkin lymphoma and B-cell non- Hodgkin's

lymphoma with respect to pathogenesis and its impact on therapeutic decisions and outcomes in such contentious cases which a clinician must face.

Keywords: Classical Hodgkin lymphoma, Large B-cell lymphoma, Chemoimmunotherapy, B-cell gene rearrangement

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INTRODUCTION

While Hodgkin's lymphoma and non-Hodgkin's lymphoma are considered distinct entities, they represent a continuous spectrum of malignant transformation of B-cells. Cases at the interface such as B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin's lymphoma, also otherwise called as "grey zone lymphoma" present diagnostic and therapeutic challenges. Additionally the presence of both Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL) either concurrently (composite lymphoma) or subsequently present the clinician with the dilemma of one tumor differentiating in two directions or two different tumors. We report a case of a 62-year-old woman with classical Hodgkin's lymphoma who subsequently developed a large B-cell non-Hodgkin's lymphoma at a different anatomic site

within two years after initial disease and six months after receiving high dose chemotherapy and autologous stem cell transplantation for her relapsed Hodgkin's lymphoma. She was subsequently treated with conventional combination chemo-immunotherapy (R-EPOCH) and responded with a near complete remission. We describe the clinico-pathologic and radiological features of this unique case which raises the question whether the two B-cell tumors arise by independent mechanisms from different precursors or have a common cell of origin that undergoes transformation over time and review the literature regarding treatment and outcome of such lymphomas.

CASE REPORT

A-62-year old woman was referred with recent finding of abdominal lymphadenopathy. She had presented to an outside institution with Hematuria. A CT scan of the abdomen and pelvis with contrast demonstrated lymphadenopathy in the retroperitoneal (RP) area leading to left hydronephrosis (Figure 1A). She also complained of B symptoms but her physical examination did not reveal any palpable lymphadenopathy or organomegaly and her laboratory results including serum LDH level were unremarkable. Management at our institution included placement of a left ureteral stent to relieve the obstruction and excisional biopsy of the retroperitoneal lymph node to characterize the underlying etiology.

The biopsy showed alteration of the nodal architecture by a nodular proliferation with thick, fibrotic septa. Marked nodal capsular fibrosis was also noted. The proliferation contained mixed inflammatory cells of small lymphocytes and histiocytes with scattered large atypical cells consistent with Reed-Sternberg (RS) cells and some variants (Figure 2A). Immunohistochemical (IHC) staining was positive for CD30 in the malignant Hodgkin's and Reed Sternberg (HRS) cells (Fig. 2B). The RS cells did not demonstrate CD15 and CD45 staining but showed variable CD20 staining (Figure 2C). The biopsy was also reviewed at the National Cancer institute (NCI) and felt to be consistent with the diagnosis of classical Hodgkin lymphoma, nodular sclerosing subtype. Molecular studies were performed for T-cell receptor and immunoglobulin light and heavy chain gene rearrangement but did not demonstrate clonal rearrangement of B or T-cells.

A staging PET scan confirmed the extensive retroperitoneal and bilateral pelvic lymphadenopathy measuring 9 x 5.4 cm with mean standard uptake values ranging between 3 and 5.7. Thus the patient was diagnosed with stage IIB classical Hodgkin lymphoma with unfavorable NCCN factors (ESR>50, > 3 lymphoid regions, B-symptoms). Hence she was treated with six cycles of ABVD (adriamycin, bleomycin, vinblastine and dacarbazine) and achieved complete remission.

She relapsed within three months of completing initial chemotherapy and after pathological confirmation received salvage chemotherapy with two cycles of ICE (ifosfamide, carboplatinum and etoposide) followed by autologous transplantation after conditioning with BEAM (carmustine, etoposide, cytarabine and melphalan). She remained in remission for nine months but developed local recurrence of Hodgkin lymphoma in the pelvis for which pelvic irradiation (3960 cGy in 22 fractions) was administered.

Surveillance PET scan at six months after finishing radiation showed decrease in the size and intensity of pelvic lymphadenopathy but demonstrated a new hypermetabolic enhancing mass approximately 4.9 x 2.8 cm in size in the vaginal cuff (Figure 1B) with new retroperitoneal, mesenteric and left inguinal lymphadenopathy. The biopsy of the vaginal mass showed sheets of large atypical cells with round to oval nuclei, finely granular chromatin and central large nucleoli (Figure 2D). IHC staining revealed bright expression of CD20 (Fig.2F), dim expression of CD30 (Figure 2E), CD79, PAX-5, OCT-2, PU.1, Bcl-2 but did not show expression of EBV RNA (EBER) by in situ hybridization in the tumor cells. B-cell gene rearrangements were investigated using IGK Gene Clonality Assay from IVS (repeated twice) and with Jk-home brew. For the heavy chain: IGH (FR2 and FR3) we used home brew (lab developed test, LDT). We checked for both immunoglobulin heavy and light chains gene rearrangements. Molecular studies demonstrated kappa light chain clonal rearrangement in the B-cells (Figure 2G). This was felt to be consistent with the diagnosis of diffuse large B-cell lymphoma (DLBCL) with CD30 expression and once again was confirmed at the NCI.

Staging confirmed stage IV DLBCL with high IPI score. Given poor response of transformed large cell lymphomas to conventional chemotherapy regimens, our patient opted to go on an investigational protocol as a result of which she received Pralatrexate (PDX, 10-propargyl 10-deazaaminopterin), a novel anti-folate drug which has been approved for treatment of relapsed or refractory peripheral T-cell lymphoma.

She was found to have progression of disease at the end of two cycles and hence her regimen was changed to an anthracycline based standard immunochemotherapy combination: R-EPOCH (rituxan, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin) of which she has received four cycles so far followed by near complete resolution of her large B-cell lymphoma (Figure 1C). We are contemplating administration of a total of six cycles of R-EPOCH and possibility of reduced intensity allogeneic transplantation while in remission to consolidate the favorable response.

DISCUSSION

We believe that the presence of persistent CD30

Figure1: A) Initial whole body FDG PET/CT scan with arrow demonstrating retroperitoneal and pelvic lymphadenopathy which are hypermetabolic with mean standard uptake value of this activity ranging between 3-5.7; B) Second whole body FDG PET/CT scan (6 months after finishing pelvic radiation for relapse of Hodgkin's lymphoma) with arrow demonstrating a new 4.8x2.6 cm hypermetabolic vaginal mass with mean standard uptake value ranging between 7.2 -11.5; C) Third whole body FDG PET /CT scan (3 weeks after finishing 4 cycles of chemo-immunotherapy with R-EPOCH) demonstrating complete resolution of the hypermetabolic vaginal mass. Anterior uptake is secondary to normal bladder activity (FDG excretion by the kidneys).

and increased CD20 expression in the vaginal mass biopsy in our patient with a previous history of cHL raises a number of questions regarding the pathogenic interrelationship and treatment of such lymphomas. Observations from small number of case reports suggest an inherent tendency of nodular lymphocyte-predominant Hodgkin's lymphoma (non-classical NLPHD) to develop DLBCL either concurrently or subsequently [1-6] with a wide range in the incidence rates (0.6-9.8%) across case series over 20 years of follow up. It is now felt that this entity is really a form of follicular lymphoma. There are also case reports of the two diseases presenting together, commonly known as "composite lymphoma" [7-9]. However, little literature exists on the association between cHL and NHL because of the rarity of this condition. The reported incidence of NHL in large series of HL survivors has ranged from 0.9% at an average follow up of 6.7 years to 1.6% at 15 years [10-12]. Diffuse large B-cell lymphoma was the most common histology reported in these studies accounting for 78 percent of the cases. The largest experience comes from the International Database on Hodgkin Lymphoma, which evaluated the course of 12,411 patients with an average follow up of 6.7 years [10]. One hundred and six cases of NHL were observed with a continuous increase in relative risk with a follow up in males (from 28.2 during the five to nine year period, to 120 during the 15

to 19 year period). In females, the risk increase was confined to the first 15 years, with a peak relative risk of 45.4 during the five to nine year observation period.

While the pathogenesis of NHL's following Hodgkin lymphoma remains unknown some authors have speculated that they both originate from a common B-cell precursor, probably a germinal center B-cell and share some common and some distinct molecular transforming events [13-15]. It is sometimes possible to demonstrate the common cell of origin with careful molecular studies. With the help of polymerase chain reaction amplification we were able to identify and characterize clonal B cells by demonstrating presence of J_k gene (joining region gene of Kappa light chain) rearrangement in the DLBCL tumor. We then generated clone-specific primers which could enable us to pick-up the same rearrangement in the HRS cells if the HRS cells and DLBCL tumor cells shared the same immunoglobulin light chain rearrangement which could provide valuable hint towards their common origin and thereby insight into the biology of such rare lymphomas. Unfortunately in our case the negative molecular studies for B-cell clonality i.e. absence of J_k gene rearrangement in the cHL tumor sample were not helpful in establishing this possibly common malignant B-cell precursor. This is not uncommon and we believe raises the possibility of the two B-cell tumors arising from different precursors. Given

Figure2: A) Initial retroperitoneal lymph node biopsy (H&E stain, oil immersion). It exhibits mixed inflammatory cells, lymphocytes and histiocytes. There are scattered large atypical cells, consistent with Reed-Sternberg cells with bizarre nuclear features; B) Initial retroperitoneal lymph node biopsy (CD30 staining, 40X.). It exhibits strong expression of CD30 in malignant HRS cells; C) Initial retroperitoneal lymph node biopsy (CD20 staining, 40X.). It exhibits few HRS cells that demonstrate weak expression of CD20; D) Vaginal mass biopsy (H&E stain, oil immersion). It exhibits diffuse lymphocytic infiltrate comprising of sheets of large lymphocytes with prominent eosinophilic nucleoli; E) Vaginal mass biopsy (CD30 staining, 40X.). It exhibits weak CD30 expression in most of the large neoplastic lymphocytes; F) Vaginal mass biopsy (CD20 staining, 40X.). It exhibits sheets of large neoplastic lymphocytes with intense CD20 expression.

Figure 3: Polymerase chain reaction (PCR) for J_k gene (joining region gene of Kappa light chain) rearrangement in cHL and DLBCL tumors; Lane 1 is the ladder; Lane 2 is the positive control for the J_k gene rearrangement, is the negative control for the J_k gene rearrangement; Lane 4 is the diffuse large B-cell lymphoma sample showing a distinct band thereby confirming the presence of J_k gene rearrangement which is a marker of clonal B cells; Lane 5 is the classical Hodgkin lymphoma sample showing a polyclonal pattern in the region of J_k gene rearrangement thereby demonstrating absence of clonal B cells.

expression of CD20 on the HRS cells in the initial biopsy, another relevant question is whether the patient should have been diagnosed with B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin's lymphoma also called as "grey zone lymphoma" per the 2008 WHO classification for mature B-cell lymphomas. The majority of HRS cells in the first biopsy showed no expression of CD45 and CD79a but over-expression of CD30 with variable CD20 staining. The neoplastic cells of grey zone lymphomas typically express CD45. CD20 and CD79a are also frequently positive, and may be strongly expressed on the majority of the tumor cells. Because of the absence of strong and uniform expression of CD20, CD79a and CD45 on the tumor cells that favor the diagnosis of grey zone lymphoma, we believe that the immunohistochemical (IHC) characteristics of the first biopsy support the diagnosis of cHL and exclude the possibility of grey zone lymphoma although variants of each category cannot be entirely ruled out. Sometimes the neoplastic HRS cells of cHL do express CD20 with a reported frequency ranging from less than 5% to more than 50% of tumors [16-19] corroborating our hypothesis. However the prognostic significance of CD20 expression in cHL remains controversial [20-

23].

There is little agreement on definitive risk factors for NHL in patients treated for HL. It is possible that the differences among studies represent differences in the patient populations examined. It is also possible that pathologic misclassification may confound results, with recurrent HL being misdiagnosed as NHL or NHL being initially diagnosed as HL. Only a few studies have included expert review of the original tissue diagnosis as part of the study [11, 24-25]. With improvement in histopathologic techniques the risk of NHL appears to have declined over the past decade. A key question that is raised in such cases is whether the development of the subsequent large cell lymphoma was triggered by the chemotherapy, radiotherapy or combination regimens used for treating the cHL and for conditioning for autotransplantation. Most of the cytotoxic agents and radiation our patient received are capable of generating single and double stranded DNA breaks (DSB). Germinal Center (GC) tumors such as cHL and some other B-cell lymphomas seem to arise because of aberrations during B-cell development processes such as somatic hypermutation, class switch recombination and may be VDJ recombination, a major feature of which is DSB. Typically secondary NHL's develop after the first five years of initial therapy of primary cancer as opposed to our patient who developed NHL within two years of initial therapy for her HL. Hence based on clinical history, morphologic pattern and immunophenotypic studies we believe that the development of the NHL in this case is consistent with a transforming event between cHL and DLBCL or a biologic evolution of a malignant B-cell clone rather than a secondary malignancy. Whether cytotoxic agents and radiation can accelerate the transforming molecular mechanisms and contribute to biological aggressiveness remains to be ascertained. A large International Database Study included 106 patient who developed NHL following a prior malignancy; combined modality treatment and any type of treatment for relapse were associated with increased risk for NHL with relative risks of 2.2 to 4.5 [24]. However, other reports have found no apparent differences in increased risk between patients treated with chemotherapy alone, radiotherapy alone, or a combination modality [12, 24, 26-27]. There are also conflicting data on the importance of host factors such as gender and age on the risk of NHL. Some studies noted no relationship between these factors and NHL [28], while the International Database and report from the Netherlands Cancer Institute found that increasing age over 30 and to a lesser degree, male sex were risk factors [10, 25]. In addition, HL may be associated with a general state of immunosuppression [29-30], which can predispose to the development of NHL as in transplant recipients. Support for this hypothesis comes from a detailed study of 14 patients who developed NHL within a median of 136 months from the diagnosis of HL [30]. The high prevalence of

extranodal sites, histology of either intermediate or high grade lymphoma, and immunophenotypic findings typical of NHL of B-cell lineage patients were similar to NHL arising in immunosuppressed patients.

Little literature exists regarding the outcome of DLBCL after treatment of cHL. Initial studies reported poor outcomes [31]. However, later studies suggest that some of these patients may be curable with aggressive multi-agent chemotherapy [3, 4, 10, 11, 26, 30]. Of the 106 patients with secondary NHL in the International Database on HL (diagnosed between 1960 and 1987), 45 were alive at the time of report with a five year probability of survival of 30 percent. To investigate the course of disease for secondary NHL, Rueffer et al. retrospectively analyzed patients treated within clinical trials of the German Hodgkin's Lymphoma Study Group (GHSG) from 1981 to 1998 [11]. At first diagnosis of HL, the pathologists rejected 114 (2.1%) of 5,520 cases initially diagnosed as HL and rediagnosed them as primary NHL. Fifty-two (0.9%) of the remaining 5,406 patients developed a secondary NHL. One patient was excluded from further analyses because of insufficient documentation. Six patients had no further therapy because of patient refusal (n = 1) or rapidly progressive disease (n = 5). For the remaining 45 patients, overall response rate was 43% (36% complete response and 7% partial response). The actuarial 2-year freedom from treatment failure (FFTF) and overall survival (OS) for all patients was 24% and 30%, respectively, and for patients with diffuse large-cell lymphoma, it was 28% and 35%, respectively. Time of occurrence of secondary NHL after first diagnosis of HD and variables employed in the age-adjusted International Prognostic Factor Index (IPFI) significantly influenced treatment outcome. A retrospective analysis of patients in the Surveillance, Epidemiology and End Results (SEER) program database treated from 2000 to 2004 reported five and ten year survival rates for patients with secondary NHL of 54 and 41 percent respectively [32]. Despite relative worse prognosis compared with those with no prior malignancy, this data suggested a strong improvement in the outcomes for NHL patients with prior malignancy between 1990-1994 (five year survival rate of 38 percent and 10 year survival rate of 24%). Until prospective long term follow up data from well-designed randomized trials comparing outcome of *de novo* DLBCL with secondary DLBCL is available to guide therapeutic decision, we believe that patients like the one in our case report should be treated with multi-agent chemotherapy regimens and enrolled in clinical trials when they fail established aggressive protocols.

Another clinical rule illustrated by this case that cannot be overemphasized is the importance of re-biopsy at disease progression or relapse specifically at an unusual previously uninvolved anatomical site. This is crucial to avoid misdiagnosis and allows effective management of this rare entity especially when whole body FDG PET/CT scan is becoming the standard of

care in the follow up of cHL patients.

CONCLUSION

While it was difficult for us to establish that the initial classical Hodgkin lymphoma and subsequent development of large B-cell non-Hodgkin's lymphoma originated from the same malignant B-cell clone either synchronously or metachronously, an important point, this case has been thought provoking and educational at various stages of its evolution. We believe that this case brings to light several key issues in such challenging series of patients: first, it should not be presumed that the outcome of secondary large B-cell lymphomas with standard chemoimmunotherapy regimens is inferior or at least different than *denovo* cases until prospective randomized data from well-designed clinical trials validates this conception. Second, while it is tempting to think that when patient's relapse from a hematologic malignancy, it is likely that this is the recurrence of the primary disease either due to residual resistant disease or further clonal evolution, this case highlights the importance of reconfirming tissue diagnosis at relapse or progression of the primary hematologic malignancy. Third, patients with Hodgkin lymphomas are always at risk of developing secondary malignancies of various phenotypes and hence active surveillance and close vigilance needs to be exercised both by the patient and by the clinician.

Author Contributions

Salvia Jain – Conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Critical revision of the article, Final approval of the version to be published

Bruce Raphael – Analysis and interpretation of data, Drafting the article, Critical revision of the article, Final approval of the version to be published

Kent Friedman

Group 1 - Conception and design, Acquisition of data, Analysis and interpretation of data, Critical revision of the article, Final approval of the version to be published

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Sherif Ibrahim – Analysis and interpretation of data, Drafting the article, Critical revision of the article, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

The authors declare no conflict of interest with an institution or product mentioned in the manuscript.

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