RESEARCH ARTICLE

Synchronous and Metachronous Malignant Epithelial and Lymphoid Tumors: a Clinicopathologic Study of 10 Patients from a Major Tertiary Care Center in Pakistan

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Abstract

Case reports and case series documenting unfortunate patients with more than one malignant neoplasm are rare but well established. While majority of such patients have two malignancies, cases with three or even four malignant neoplasms in the same patient have been published in literature. A number of factors influencing carcinogenesis have been implicated in such cases including exposure to large amounts of radiation, chemotherapy for the original malignancy; prolonged history of heavy smoking and exposure to other environmental carcinogens; aging; and underlying genetic alterations. Concomitant multiple malignant neoplasms may be ***synchronous***-two or more malignant neoplasms histologically distinct from each other, arising in the same site and detected simultaneously (for example during the same hospital admission) or detected one after the other in sequence in a period less than 6 months; or **metachronous**-two or more malignant neoplasms of similar or distinct histologic type detected at different times (after an interval of greater than 6 months) in different anatomic sites. Any combination of malignant tumors can occur in the same patient for example carcinomas with other carcinomas, carcinomas with Non-Hodgkin or Hodgkin lymphomas, carcinomas with mesotheliomas, carcinomas with sarcomas etc. We have reported several cases with multiple malignancies during our practice, and these cases were composed of the different combinations described above. The aim of the present study is to document 10 such cases of combined carcinoma and Non Hodgkin lymphoma in the same patient which were diagnosed in our section.

Keywords: Carcinoma- lymphoma- synchronous- metachronous- concomitant- malignancy

Asian Pac J Cancer Prev, **18 (8)**, 2067-2072

Introduction

Case reports and case series documenting unfortunate patients with more than one malignant neoplasm are rare but well established. While majority of such patients have two malignancies, cases with three or even four malignant neoplasms in the same patient have been published in literature (Hashimoto et al., 1988; Porta et al., 1994; Nagane et al., 1996; Mukai et al., 2001; Takada et al., 2002; Zahumensky et al., 2007). A number of factors influencing carcinogenesis have been implicated in such cases including exposure to large amounts of radiation-at least 2 of such patients had been exposed to and survived the atomic bomb explosion in Hiroshima, Japan in 1945; chemotherapy for the original malignancy; prolonged history of heavy smoking and exposure to other environmental carcinogens; aging; and underlying genetic alterations (Hashimoto et al., 1988; Nagane et al., 1996; Takada et al., 2002; Zahmensky et al., 2007). Some malignant neoplasms such as renal cell carcinoma and hepatocellular carcinoma are not uncommonly associated with the development of concomitant or subsequent malignancies at other sites (Nzeako et al., 1994; Beisland et al., 2006; Fernandez-Ruiz et al., 2009). Similarly, the development of malignant neoplasms such as breast carcinoma, colon carcinoma etc, sometimes after years or even decades is not uncommon in patients with Non Hodgkin or Hodgkin lymphomas, germ cell tumors (seminomas) etc who have been treated for the primary tumor with chemotherapy or radiation therapy (Cutuli et al., 1997; Cutuli et al., 2001; Foss et al., 2002; Bhatia et al., 2003; Hughes et al., 2003; Kochbati et al., 2003; ben Hassouna et al., 2007; Geffen et al., 2007; hemminki et al., 2008). Concomitant multiple malignant neoplasms may be **synchronous**-two or more malignant neoplasms histologically distinct from each other, arising in the same site and detected simultaneously (for example during the same hospital admission) or detected one after the other in sequence in a period less than 6 months; or **metachronous**-two or more malignant neoplasms of similar or distinct histologic type detected at different times (after an interval of greater than 6 months) in different anatomic sites (Kileiksiz et al.,2007). Any combination of malignant tumors can occur in the same patient for

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example carcinomas with other carcinomas, carcinomas with Non-Hodgkin or Hodgkin lymphomas, carcinomas with mesotheliomas, carcinomas with sarcomas etc. We have reported several cases with multiple malignancies during our practice in the largest center for Histopathology in Pakistan and these cases were composed of the different combinations described above. The aim of the present study is to document 10 such cases of combined carcinoma and Non Hodgkin lymphoma in the same patient which were diagnosed in our section.

Meterials and Methods

Surgical Pathology files of patients with more than one malignant tumor diagnosed in the Section of Histopathology, Department of Pathology and Laboratory Medicine, Aga Khan University Hospital were retrieved. Slides of all cases were reviewed by the two principal authors (ZA and NU). Demographic data was also abstracted from the records. Statistical analysis was performed using SPSS 11.0 software. Verbal consent was obtained from all the patients at the time of taking follow up. None of the patients had any objection to inclusion in the study. No patient identification was revealed in the study.

Results

Of the 10 cases documented here, 7 (70%) patients were males and 3 (30%) were females. Ages of the patients ranged from 14 to 81 years with mean and median ages of 60.8 years and 62 years respectively. Of the 10 cases, 5 (50%) were synchronous and 5 (50%) were metachronous. The clinical and morphological details of all 10 patients are shown in Table 1. Follow up was available in 8 out of 10 cases. Of the 8 patients, 5 are alive and apparently well while 3 died of their disease (Table 1).

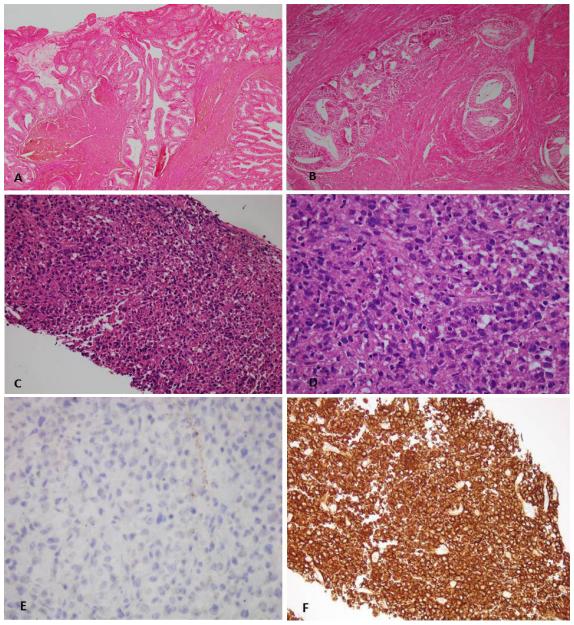

Figure 1. A, B). Endometrioid adenocarcinoma composed of complex fused glands invading into the myometrium. C, D) Core biopsy of liver showed a cellular infiltrate arranged in diffuse sheets. E, F) This infiltrate is negative for Cytokeratin AE1/AE3 and diffusely positive for CD20 immunostain

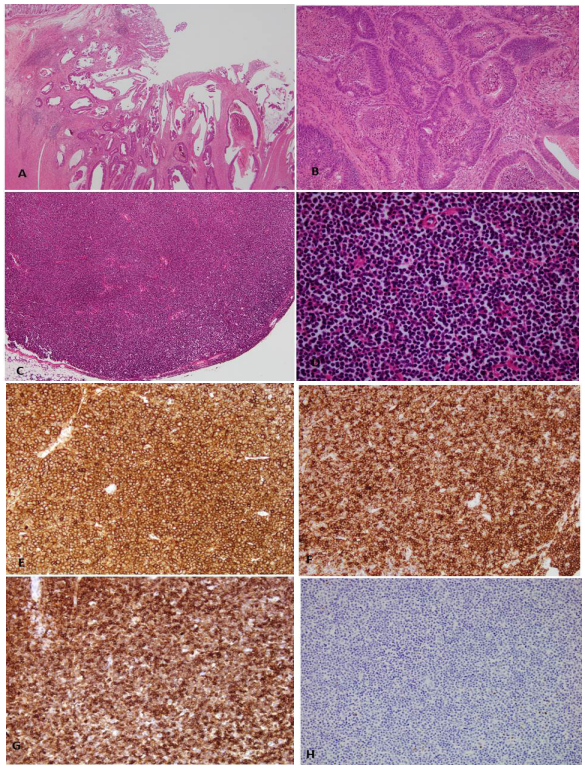

Figure 2. A, B) Large bowel wall exhibiting an infiltrating moderately differentiated adenocarcinoma. Garland type necrosis is seen within glandular lumina. C, D) Low and high power examination of lymph node showed effaced nodal architecture by a monotonous population of small lymphocytes. E, F, G) The lymphoid population is positive for CD20, CD23 and CD5 immnuostains respectively. H). Negative cyclin D1 in tumor cells.

Discussion

The oldest record we found of a patient with multiple malignancies was the report of an unusual case published in 1978 documenting an unfortunate lady with no less than four primary tumors-carcinoma of breast, liposarcoma, Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (Kornberg et al., 1978). The association between carcinoma and Non Hodgkin lymphoma is well known and a number of case reports and series have been published

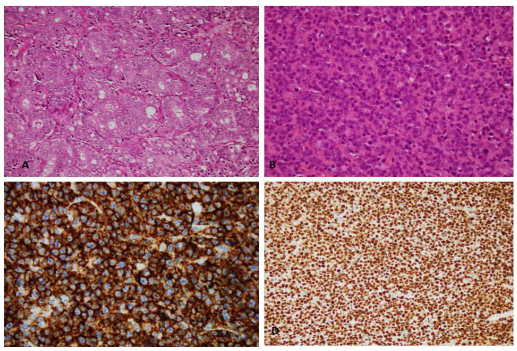

Figure 3. A) Prostatic adenocarcinoma with fused glands. B). The radius bone biopsy showed a cellular infiltrate arranged in sheets and composed of large lymphoid cells. C). Diffuse strong CD20 positivity in tumor cells with D) high proliferating index (Ki 67).

Table 1. Clinical and Morphological Details of Patients with Carcinoma and Lymphoma (N=10)

S. No	Sex	Age (in years)	Synchronous/ Metachronous	Site of tumor	Year & type of biopsy/ resection	Carcinoma characteristics	Lymphoma characteristics	Follow up
1	F	81	Metachronous	-Uterus (endometrium) -Liver (multiple liver lesions)	2008 Resection :Total abdominal hysterectomy & bilateral salpingo-oophorectomy (TAH BSO) -Core biopsy of liver	Endometrioid Adenocarcinoma,FIGO grade II, FIGO stage IC [Fig 1A,B] Other lesions -Simple endometrial hyperplasia without atypia -Adenomyoma	Diffuse large B cell lymphoma of liver [Fig 1C-F] IHC profile : LCA, CD20: Positive CD3,CD5,Cyclin D1,EMA,CK Cam 5.2, CK AE1/AE3 Negative	Received chemo and radiotherapy. Died of disease in March 2016
2	F	64	Synchronous	Left breast -Left axillary lymph nodes	Modified radical mastectomy in 2009	Invasive ductal carcinoma, grade II; Tumor size 3.5x3 x2.8cm. Deep margin tumor free. 2/21 lymph nodes positive for metastatic carcinoma pTNM: pT2,N1,Mx	9/21 of Lt axillary LNs: Nodal marginal zone B cell lymphoma IHC CD20,CD43, Bcl2 :positive CD3,CD21,CKAE1/AE3: negative	Lost to follow up
3	F	62	Synchronous -H/O IDC Lt breast (record of biopsy not available) -H/O Hodgkin lymphoma 15 years back treated with chemotherapy (no record of diagnosis or treatment available)	-Right modified radical mastectomy (MRM) -Left MRM	-2010 -2010	Right MRM: Invasive ductal carcinoma, grade II; Tumor size 2x1.5x1cm. Deep margin tumor free. All 7 lymph nodes negative for metastatic carcinoma ; pTNM: pT2,N0,Mx Left MRM: Breast: No residual tumor. All 21 lymph nodes (LNs) negative for metastatic carcinoma.	2/21 of Left axillary and 4/7 right axillary LNs positive: Nodal marginal zone B cell lymphoma IHC CD20,CD43, Bcl2 :positive CD3,CD15,CD5,CD30,CD43,CD10,CKAE1/AE3 :negative	Bilateral MRM. Chemotherapy given along with Herceptin for 1 ½ years. Oral chlorambucil, 5 cycles given for lymphoma. Died of disease 6 years after diagnosis.
4	M	65	Synchronous	Rt hemicoloectomy	2014	Exophytic and ulcerating Moderatley differentiated adenocarcinoma. All 16 LNs negative for metastatic carcinoma [Fig 2A,B] pTNM: pT3,N0,Mx	All 16 LNs involved by small lymphocytic lymphoma/Chronic lymphocytic leukemia (SLL/CLL) [Fig 2C-H] IHC CD20,CD5,CD23,Bcl2 :positive CD3,Cyclin D1 :negative	Lost to follow up
5	M	14	Synchronous	-Lt colon (Descending & sigmoid) [Adenocarcinoma] -Rt colon (ileum & cecum) [DLBCL]	-2014 (Lt hemicolectomy) -2014 (Rt hemicolectomy)	Ulcerated mass. Moderately differentiated mucin secreting adenocarcinoma. Metastatic carcinoma involving 10/10 LNs pTNM:pT4a,N1a,Mx	Diffuse large B cell lymphoma (DLBCL) IHC: CD20 :positive,ki67 70%; CD3,Tdt,CD10: negative	Recurrence at colostomy site. Received 1 cycle of R-CHOP chemotherapy. Died 3 months after diagnosis.
6	M	61	Metachronous	-Left cervical lymph nodes (LN) -Prostate -Lt axillary LN	-2014 excision of LN -2015 Needle biopsies(12) -2016 Excision of LN	-Prostatic adenocarcinoma in Lt mid-1, mid 2, base 1 and base 2. Gleason major 3, minor 3; score 3+3=6 Average 40% of cores involved by tumor. Perineurial invasion not seen.	Both Lt cervical & Lt axillary LNs (excised in 2014 & 2016)showed DLBCL/Follicular lymphoma, Grade II IHC CD20,CD10, BCL2,BCL6,CD21,CD23: positive, ki67 60-70% CD3,Cyclin D1, CD5: negative	-8 cycles of CHOP and 2 cycles of Bendamustine given for follicular lymphoma-Radiation given for follicular lymphoma -Recent four PET scans normal. -Patient is alive & well.
7	M	76	Metachronous	-Prostate -Right radius bone (pathological fracture)	-2014 -Transurethral resection of prostate(TURP) -2016 Biopsy Rt radius bone	-Prostatic adenocarcinoma, Gleason major 4, minor 4; Score 4+4=8, involving approximately 60% of submitted tissue.	Diffuse large B cell lymphoma	Received no treatment either for prostatic adenocarcinoma or DLBCL due to non-compliance. Patient is so far alive and well.
8	M	76	Synchronous	Sigmoid colon with lymph nodes (LNs)	2016 Lt hemicolectomy	-Exophytic tumor. Moderately differentiated adenocarcinoma. 2/24 LNs involved by metastatic carcinoma pTNM:pT3,pN1,Mx	Many of the 24 LNs involved by SLL/CLL IHC CD20,CD5,CD23,Bcl2 :positive, Ki67 10% CD3,Cyclin D1 negative	No treatment given. Died 2 months after diagnosis.

Table 1. Continued

S. No	Sex	Age (in years)	Synchronous/ Metachronous	Site of tumor	Year and type of biopsy/ resection	Carcinoma characteristics	Lymphoma characteristics	Follow up
9	M	76	metachronous	Hip bone Prostate	2016 hip bone biopsy 2016 TURP	Prostatic adenocarcinoma, Gleason major 3, minor 4; Score 3+4=7, involving approximately 5-10% of submitted tissue.	Hip bone as well as prostate involved by SLL/CLL IHC CD20,CD5,CD23,Bcl2 :positive, Ki67 10% CD3,Mum 1,CD56, CD10 & Cyclin D1 negative	No treatment yet offered. Patient is alive and well.
10	M	49	Metachronous	Right Kidney Para-aortic lymph node	2015 Right radical nephrectomy 2016 Lymph node core biopsy	Clear cell renal cell carcinoma, Fuhrman nuclear grade II, All 22 perihilar lymph nodes negative for metastatic carcinoma pTNM:pT1a,N0,Mx	Diffuse large B cell lymphoma of para-aortic lymph node IHC: LCA,CD20,BCL2, Mum 1: positive; CD3, CD10,CD5,CD30, Cytokeratin AE1/AE3 negative. Ki67 60-70%	No treatment received for renal cell carcinoma; Received one cycle of tailored chemotherapy for DLBCL

over the years documenting such occurrence in the same patient in various organs in synchronous or metachronous fashion. Some combinations are relatively more common: for example, the combinations, either synchronous or metachronous of a gastric adenocarcinoma and low grade B cell lymphoma of mucosa associated lymphoid tissue (MALT) has been repeatedly reported. The important role of Helicobacter Pylori infection in the etiology and development of such double malignancies has been highlighted. It is believed that in such cases, especially if synchronous, lymphomas develop before carcinomas but prognosis is more closely associated with gastric adenocarcinomas (Nakamura et al., 1997; Vaiphei et al., 1999; Lee et al., 2005; Seo et al., 2007; Ioannidis et al., 2013). In one case, a primary gastric MALT lymphoma in a patient with H.Pylori infection regressed after eradication of H.Pylori infection and surgical resection of the tumor. However, the patient developed gastric adenocarcinoma on follow up while was temporally associated with reinfection with H.Pylori (Ghoshad et al., 2002). Patients with gastric MALT lymphoma and a concomitant autoimmune disease are also at increased risk for development of gastric carcinoma and need to be closely followed up after remission of the MALT lymphoma (Raderer et al., 2003). Interestingly, none of our 10 cases involved the stomach. Conversely 3 out of our 10 cases involved the colon. Of these 3 patients (Table 1), 2 had adenocarcinoma in cecum and sigmoid colon respectively and both had small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL) in the regional lymph nodes. The third patient, a 14 year old boy had a colonic adenocarcinoma in sigmoid colon and a diffuse large B cell lymphoma (DLBCL) in the cecum. Unlike stomach, there are few case reports documenting colonic adenocarcinoma and lymphoma in the same patient (Mannweiler et al., 2003; Bhanote et al., 2005). Of our 10 cases, 2 involved the breast. One of these patients had invasive ductal carcinoma of the left breast. While all the recovered lymph nodes were negative for metastatic carcinoma, several showed B cell nodal marginal zone lymphoma. The other patient had had left mastectomy for invasive ductal carcinoma of left breast. After several years, she also developed carcinoma in the right breast and concomitantly developed enlarged left axillary lymph nodes. She underwent right modified radical mastectomy for invasive ductal carcinoma in the right breast and the enlarged left axillary lymph nodes were also resected. The resected enlarged left axillary lymph nodes showed a B cell marginal zone lymphoma. Interestingly, both patients developed low grade B cell nodal marginal zone lymphoma. There are several case reports in literature documenting simultaneous occurrence of breast carcinoma and malignant lymphoma, either in the breast itself or in the axillary lymph nodes (Quilon et al., 2006; Cheung et al., 2007; Miles and Jacimore., 2012). Two of our patients had a combination of prostatic adenocarcinoma and non-hodgkin lymphoma. The latter, interestingly, in both cases involved a bone. There have been case reports in literature which have shown such combinations both synchronously and metachronously (Gros et al., 1984; Terris et al., 1997; Alongi et al., 2010). The lymphomas mostly have been low grade such as MALT lymphoma or SLL. One of our cases also had SLL. However, the other patient with prostatic adenocarcinoma had an associated DLBCL. One of our patients had a combination of renal cell carcinoma (RCC) and DLBCL. A number of studies have reported the frequent association between RCC and NHL (Nzeako et al., 1994; Anderson et al., 1998; Kurtz et al., 1999;Beisland et al., 2006). These studies in addition to confirming such association was not uncommon demonstrated that the observed rates of RCC developing in patients with NHL, and the observed rates of NHL developing in patients with RCC were greater than expected and statistically significant.

The occurrence of multiple malignancies in some unfortunate patients (even four to five in a single patient) may be due to a certain extent related to an inherent increased predisposition of such patients to develop multiple malignancies but chemotherapy, previous treatment with cyclophosphamide and radiation therapy may also be contributing factors (Rohde and Jakse., 1998). A competent immune system is important in the prevention of cancers and therapeutic or disease induced suppression of the immune system may increase the

risk of development of a second malignancy in patients already suffering from cancer (Hemminki et al., 2003; Barzilai et al., 2006). Infectious agents such as viruses have been implicated in increasing the risk for developing a second malignancy in cancer patients. A case of rectal squamous cell carcinoma and metachronous diffuse large B cell lymphoma was recently reported in an HIV infected patient (Choi et al., 2014). Exposure to ultraviolet light has also been implicated in causing non Hodgkin lymphoma and skin cancer in the same patients and in one study their occurrence was strongly associated with each other (Anderson et al., 1998). The incidence rate of multiple malignancies varies according to age of patients, gender, geographic locales, site of tumor and type of malignancies. Multiple factors may be involved in the pathogenesis and as discussed above, genetic predisposition, chemotherapy and radiation therapy, immunodeficiency, infectious agents etc may all be involved (Adami et al., 1995; Fonseca et al., 2015). Exposure to asbestos greatly increases the risk of developing lung cancer and mesothelioma and there are published case reports documenting concurrent, synchronous adenocarcinoma of lung and malignant mesothelioma in patients with history of asbestos exposure (Attanoos et al., 2003). As survival rates among childhood cancer patients are increasing, the risk of developing secondary malignancies years later is also increasing. Studies have shown that childhood cancer survivors are at increased risk for developing secondary malignancies compared to general population. Such risk is substantial and independently associated with multiple factors including childhood cancer at a young age, childhood Hodgkin lymphoma or soft tissue sarcoma, female gender, exposure to alkylating agents etc (Henderson et al., 2007; Hemminki et al., 2008; Meadows et al., 2009).

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