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Cutaneous Lymphoma: A Descriptive Study from a Regional Cancer Centre in South India

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Abstract:
Background: *Cutaneous lymphoma is the second most common extra nodal lymphoma with unique clinical presentation, distinct morphological and immunohistochemical features. The aim of this study was to determine the relative frequency and distribution of cutaneous lymphomas, both primary and secondary, according to the World Health Organization (WHO) 2008 and WHO-EORTC (European Organization for the Research and Treatment of Cancer) 2005 classifications.*
Methods:*A total of 37 patients were studied retrospectively during a 10 year-period (March 2006-2016) from a regional cancer centre in South India.*
Results:*The patients included 24 males and 13 females and the mean age of diagnosis was 41 years. The lesions most commonly involved the trunk (32.4%) with nodules being the most common form of clinical presentation. Primary and secondary cutaneous lymphomas constituted 75.6% and 24.4% of all cases respectively. Cutaneous T-cell lymphomas (50%) outnumbered the cutaneous B-cell lymphomas (32.1%) with mycosis fungoides (MF) and cutaneous diffuse large B-cell lymphoma(DLBCL) being the most common T and B-cell lymphoma subtypes respectively.*
Conclusion:*In comparison with other studies in the English medical literature, this study revealed relatively lower rates of mycosis fungoides (MF) and higher rates of cutaneous DLBCL. We also report two cases of blasticplasmacytoid dendritic cell neoplasm (BPDCN), not otherwise reported by any other Indian study on cutaneous lymphomas.*
Keywords: *cutaneous lymphoma, extranodal,non-Hodgkin*

I. Introduction

Cutaneous lymphoma is defined as lymphoma involving the skin as the primary and only site of involvement, or secondary involvement of the skin as a secondary site of disease. Primary and secondary cutaneous lymphoma differ in their clinical characteristics. The skin is the second most common site of extranodal lymphoma, following the gastrointestinal tract [1].

The incidence of primary cutaneous lymphoma has been estimated to be 1:1,00,000 according to WHO [2]. The aim of this study is to record the distribution, frequency and clinicopathological profile of cutaneous lymphoma along with immunohistochemical findings. This study was conducted in a regional cancer centre in South India and we compared our findings with the previously published studies in the English medical literature.

II. Materials And Methods

A retrospective analysis of all patients with cutaneous lymphomas diagnosed and treated in our institute from March 2006 to March 2016 was done.

Clinical characteristics such as age, gender, duration, location, characteristics of lesion and haematological parameters were obtained from the hospital records. The histological and immunohistochemical findings of all the cases were analysed. IHC was performed by immunoperoxidase staining on formalin fixed paraffin embedded (FFPE) tissue sections of skin biopsies using Super Sensitive^{TM} polymer-HRP Detection System. The following antibodies were used according to the histomorphological features:CD3, CD4, CD5, CD7, CD8, CD10, CD19, CD20, CD45, CD56, CD64, CD68,CD79a, CD117, BCL2, BCL6,Tdt, MPO, MUM1,

PAX5, LMP1, EMA, Ki67, CD123, BDCA-2 and PD-1, of which the last three immunomarkers were done elsewhere.

The cases which we studied were diagnosed in accordance with the 2008 World Health Organization (WHO) and 2005 WHO-EORTC (European Organisation for Research and Treatment of Cancer) classifications of cutaneous lymphoma.

III. Results

3.1 Proportion

Cutaneous lymphomas constituted 1.2% of all Non-Hodgkin lymphomas (NHL) diagnosed at our centre from March 2006-2016.

3.2 Clinicopathological characteristics

The important clinicopathological characteristics are outlined in Table-1.

Of the37 cases studied, 24 (64.9%) were males and 13 (35.1%) were females with the male:female ratio being 1.8:1. The patients were aged between 14 months to 84 years (mean, 41 years).

Lesions were most commonly seen on the trunk (32.4%),followed by the extremities (29.7%), although multiple sites in any anatomic location could also be involved.The duration of the presenting symptoms ranged from 10 days to 2 years. All the cases of immature hematopoietic malignancies and a majority (77.8%) of secondary cutaneous lymphomas presented as nodules, whereas most Mature T/NK cell lymphomas presented as patches and/or plaques.

3.3 Case frequency:

The frequency of cutaneous lymphoma is summarised in Table-2.

Of the 37 cutaneous lymphoma cases studied, 28 (75.6%) were primary cutaneous lymphoma (PCL) and 9 (24.4%) were those of secondary involvement. Mature T/NK cell lymphoma were the most common type of PCL (50%) followed by mature B cell lymphoma (32.1%) and immature hematopoietic neoplasms (17.9%).

Among the mature T/NK cell lymphomas, mycosis fungoides (MF) was the most common type (42.9%). This was followed by primary cutaneous anaplastic large cell lymphoma (C-ALCL) and primary cutaneous peripheral T-cell lymphoma, unspecified (PTL) amounting to 21.4% and 14.2% respectively. Sezary syndrome (SS), Extranodal NK/T cell lymphoma, nasal type and subcutaneous panniculitis-like T-cell lymphoma (SPTCL) constituted 1 case each in our study.

Cutaneous diffuse large B-cell lymphoma (DLBCL) was the most common subtype (66.7%) among the mature B cell lymphomas followed by primary cutaneous follicle centre lymphoma (PCFCL) (33.3%).

In the group of immature haematopoietic neoplasms, we noted 2 cases of blasticplasmacytoid dendritic cell neoplasm (BPDCN) and 2 cases of isolated myeloid sarcoma constituting 40% each. One case of primary B-lymphoblastic lymphoma (B-LBL) of the scalp was also identified.

Nine cases of secondary cutaneous lymphomas (SCL) were seen, among which systemic anaplastic large cell lymphoma (ALCL) constituted 44.4% cases, followed by follicular lymphoma (FL) accounting for 22.2%. Cutaneous involvement by lymphoblastic leukaemia was noted in 2 cases and by myeloid in 1 case.

IV. Discussion

In this study we calculated the frequency and distribution of cutaneous lymphomas in our institute from March 2006 to March 2016 using the WHO (2008) and WHO-EORTC (2005) classifications. This was also compared (Table-3) with the studies by Han et al. (Korea)[3],Bradford et al. (USA) [4], Naeini et al. (Iran) [5], Doshi et al.(India 2011) [6] and George et al. (India 1999) [7].

A total of 37 cases of cutaneous lymphomas were studied. Most of the caseswere commonly seen in 3rd, 4th and 5thdecades with a mean age of 41 years. A male predominance was noted in both primary and secondary cutaneous lymphomas. With respect to age and gender, the results of our study were similar to those of previous reports[3,4,6,7] except for a study from Iran [5] which reported an increased incidence in females. The youngest patient of primary cutaneous lymphoma encountered in our study was a 7 year old child with SPTCL.

The incidence of PCL and SCL in our study was 75.6% and 24.4% which is almost similar to the findings of a Korean study (73.1% and 26.1%) [3].

4.1 Primary Cutaneous Lymphoma (PCL)

In the present study, mature T/NK cell neoplasms constituted majority of cases which was similar to other published data [3,4,5,6,7].

4.1.1 Mycosis fungoides (MF)

Out of 6 cases of MF (Fig. 1.1), 4 cases presented with patches and the other 2 presented with both patches and plaques. The lesions were multiple and were located predominantly in the extremities and head and neck (Table-1).The incidence of MF is lower when compared to other studies. This might be explained by the presence of hospitals with specialised dermatology departments in the vicinity and only patients needing specialised chemotherapy being referred to our institute.One case of MF was classified as granulomatous MF and the rest as classical MF. The prognosis and clinical significance of granulomatous reaction in MF remains uncertain [8].

4.1.2 Sezary syndrome (SS)

One case of Sezary syndrome, which is a rare variant of cutaneous T-cell lymphoma (CTCL), was also seen. The patient presented with characteristic erythroderma and keratotic plaques on the palms and soles. The presence of CD3+, CD4+, CD8- phenotype in the neoplastic cells in skin biopsy was correlated with circulating Sezary cells with cerebriform nuclei.

4.1.3 Primary cutaneous anaplastic large-cell lymphoma (C-ALCL)

C-ALCL, a primary cutaneous CD30+ T-Cell lymphoproliferative disorder, is the second most common form of CTCL [2]. In our study, C-ALCL also was the second most common cutaneous lymphoma amongst the T-cell group. Of the 3 cases (23%) of C-ALCL, one was seen in a child. All our cases showed sheets of medium to large pleomorphic anaplastic cells with occasional hallmark cells in the dermis. Mitoses were infrequent. On immunohistochemistry, the majority of anaplastic cells were positive for CD30 and negative for ALK and EMA. We did not encounter any case of lymphomatoidpapulosis.

4.1.4 Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)

We had one case of SPTCL in a child, which is an uncommon age group of presentation.The patient presented with plaques on the thighs and abdomen and biopsy showed subcutaneous adipose tissue infiltrated by atypical lymphoid cells of different sizes (Fig. 1.2). SPTCL is derived from cytotoxic T cells of αß phenotype. The subcutaneous fat showed rimming of adipocytes by small to medium sized lymphocytes with irregular nuclei.Tumor cells were characteristically positive for CD3, CD8 and negative for CD4.

4.1.5 Extranodal NK/T cell lymphoma, nasal type

The only case of extranodal NK/T cell lymphoma, nasal type, in the present study showed infiltration of medium sized lymphocytes with irregular nuclei into the dermis and subcutis with angiodestruction. The mitotic rate was high and EBER was positive. The frequency of extranodal NK/T cell lymphoma, nasal type, was much higher in the Korean study[3] as compared to both our study and the study by Doshi et al[6].

4.1.6 Primary cutaneous peripheral T-cell lymphoma, unspecified (PTL)

In the present study, 2 cases of primary cutaneous T-cell lymphoma, unspecified, were seen. Primary cutaneous PTL belong to a heterogeneous group of PCL which do not fit into any other subtypes of lymphoma/leukaemia.They are rare, and constitute less than 10% of all CTCL[9].In the present study they constituted 14.2 % of all the CTCL, which was almost similar to the results of the Korean study (13.8%) [3]. Bothour cases were positive for CD3 and negative for CD4 and CD8.

4.1.7 Primary cutaneous follicle centre cell lymphoma (PCFCL)

Three cases of primary cutaneous follicle centre lymphoma were noted in our study. These lymphomas were composed of centrocytes with admixed centroblasts (Fig. 2.1). BCL2 was positive in one case but BCL6 was positive in all three cases.BCL2 expression, classically seen and pathognomonic of most nodal follicular lymphomas, is lacking in most cases of PCFCL. The neoplastic cells express BCL6 but CD 10 expression is variable[10]. In cases with strong positive BCL2 expression it is necessary to exclude the secondary involvement of skin by systemic/nodal follicular lymphoma.

4.1.8 Cutaneous diffuse large B-cell lymphoma (DLBCL)

Six cases of cutaneous DLBCL (Fig. 2.2) were identified in our study of which one was DLBCL, leg-type and the other five were categorised as DLBCL, other. Most cases of primary cutaneous DLBCL are either follicle centre with diffuse/large cell transformed type, or of the leg type [10]. The lymphomas characterised as cutaneous DLBCL, other, neither have features of DLBCL, leg type, nor of follicle centre lymphomas. Strong positivity for BCL2 with BCL6+, MUM1+ and CD10- point towards the diagnosis of DLBCL, leg type. On the other hand weak variable positivity for BCL6, CD10 and absence of MUM1 expression favour the diagnosis of Cutaneous DLBCL [11]. Cutaneous DLBCL constituted 21.4% of all cases of PCL in our study which was higher as compared to the studies conducted in Korea (6.1%) and USA (11.4%).
We did not come across any case of cutaneous marginal zone lymphoma.

Among the immature hematopoietic neoplasms, we encountered 2 cases of BPDCN, 2 cases of isolated myeloid sarcomaand one case of primary B-LBL in the present study.

4.1.9 Blasticplasmacytoid dendritic cell neoplasm (BPDCN)

Very few case reports of BPDCN have been described in medical literature. In the present study, BPDCN comprised 5% of all the cases. The study by Doshi et al. did not have any case of BPDCN[6], whereas BPDCN constituted 0.2% and 2.1% cases in the studies conducted in USA and Korea respectively[3,4]. BPDCN, formerly known as CD4+/CD56+ hematodermic neoplasm is a rare hematologic disorder characterised by clonal proliferation of immature precursors of plasmacytoid dendritic cells (PDC)[1,12]. It is now classified under AML and related precursor neoplasms in the 2008 WHO classification of tumors of hematopoietic and lymphoid tissue. It is most commonly seen in the sixth decade[1]. Among the 2 cases of BPDCN in our study, a point of interest was the occurrence of one case of BPDCN in the paediatric age group. Both our cases showed positivity for CD4, CD56 and CD123 (Fig. 3) with negativity for all lineage specific markers. Both cases showed bone marrow involvement. The paediatric case was Tdt positive and BDCA-2 negative, which carries a favourable prognosis[13].

4.1.10 Primary B-lymphoblastic lymphoma (B-LBL)

A single case of primary B-LBL was noted in our study, which is a rare disease.Histologically, B-LBL must be differentiated from other high-grade lymphoid tumors and small "blue round cell" tumors[14]. Our case was that of an 18 year old girl who showed CD20 and Tdt positive tumor cells with no systemic involvement at the time of presentation.

4.1.11 Myeloid Sarcoma

We also encountered two cases of isolated myeloid sarcoma which was not described in any other studies of cutaneous lymphomas. Diffuse pattern of infiltration of mononuclear cells was seen in all cases, with neoplastic cells being positive for MPO and CD117 and negative for Tdt, B-cell and T-cell markers.

4.2Secondary Cutaneous Lymphoma (SCL)

Secondary cutaneous involvement constituted 25% of all cutaneous lymphomas. We had four cases of cutaneous involvement by primary extracutaneous T-cell lymphoma (ALCL). This was followed by 2 cases of involvement by extracutaneous B-cell lymphoma (FL). Among the 3 cases of cutaneous involvement by leukaemia, 2 were those of lymphoblastic leukaemia and the other one was myeloid. All four cases of extranodal ALCL were positive for EMA, CD3 and CD30 and negative for ALK.

V. Figures And Tables

Table-1: Clinicopathological characteristics of cutaneous lymphoma

	Mature T-cell and NK-cell neoplasms	Mature B-cell neoplasms	Immature hematopoietic malignancies	Secondary
SEX				
Male	9	5	3	7
Female	5	4	2	2
AGE				
Range	7-84 years	35-77 years	11-74 years	14 months to 75 years
CLINICAL MANIFESTATION				
Patch	4	0	0	2
Plaque	2	0	0	0
Patches and plaques	2	0	0	0
Nodules	6	9	5	7
ANATOMIC LOCATION				
Head & Neck	2	3	1	3
Extremities	3	4	0	4
Trunk	6	2	2	2
Multiple	3	0	2	0

Table-2: Frequency of cutaneous lymphoma

	Total cases	Primary	Secondary
Mature T-cell and NK-cell Neoplasms			
Mycosis fungoides (MF)	6	6	0
Sezary syndrome (SS)	1	1	0
Primary cutaneous anaplastic large cell lymphoma (C-ALCL)	7	3	4
Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)	1	1	0
Extranodal NK-/T-cell lymphoma, nasal type	1	1	0
Primary cutaneous peripheral T-cell lymphoma, unspecified (PTL)	2	2	0
Mature B-cell Neoplasms			
Cutaneous follicle centre lymphoma	3	3	0
Cutaneous diffuse large B-cell lymphoma (DLBCL), leg type	1	1	0
Cutaneous diffuse large B-cell lymphoma, others	5	5	0
Follicular lymphoma (FL)	2	0	2
Immature hematopoietic malignancies			
Blasticplasmacytoid dendritic cell neoplasm (BPDCN)	2	2	0
T-lymphoblastic leukemia/lymphoma (T-LBL)	1	0	1
B-lymphoblastic lymphoma/leukemia (B-LBL)	2	1	1
Myeloid leukaemia	3	2	1

Table-3: Comparison of relative frequency of primary cutaneous lymphomas with reported incidences in other studies

	Korea[3](%)	USA[4] (%)	Iran[5] (%)	India– Doshiet al. [6] (%)	India-George et al. [7] using REAL classification (%)	Present
Primary Cutaneous lymphoma	73.1					75.6
Secondary Cutaneous lymphoma	26.1					24.4
Mature T/NK cell lymphoma	82.3	71.3	95.6	94.3	60.6	50
MF	30.4	38.3	86.9	73.4	55.5	21.4
SS	0.3	0.8	4	1.41		3.6
CD30+	16.9	10.2	3	19.1	3	10.7 (C-ALCL)
SPTCL	8.2	0.6	0	0		3.6
PTL	18	20.8	1	0		7.1
NK/T	8.2	0.3	1	0.7		3.6
AITL	0.3	0.2	0	0		0
Mature B-cell lymphoma	13	28.5	3	5.67	21.2	32.1
MZL	5	7.1	1	NA		0
FCL	1.1	8.5	2	NA		10.7
DLBCL	6.1	11.4	0	NA		21.4
Immature hematopoietic neoplasm	4	0.3	1	0		17.9
BPDCN	2.7	0.2	0	0		7.1
T-LBL	0.5	0	0	0		0
B-LBL	0.8	0.1	1	0		3.6
Myeloid sarcoma	0	0	0	0		7.1
Others	0.8	1.5	0	0		0

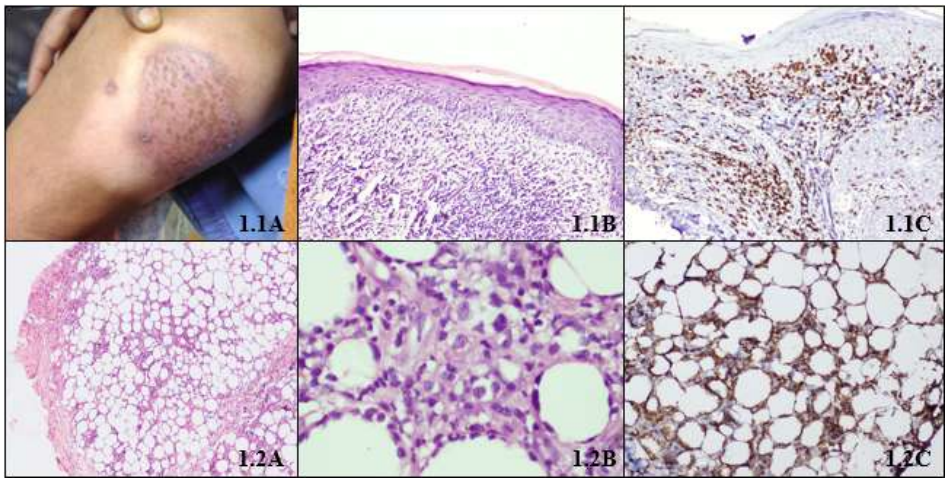

Fig 1.1 Mycosis fungoides (MF). A- Plaque of Mycosis fungoides over thigh. B- Biopsy showing intra-dermal and dermal lymphoid infiltrate. C- CD3 positive neoplastic cells. Fig 1.2 Subcutaneous T-cell panniculitis (SPTCL). A- Lobular panniculitis like infiltrate of neoplastic cells. B- Large atypical cells rimming the fat lobules. C- CD8 positive neoplastic cells.

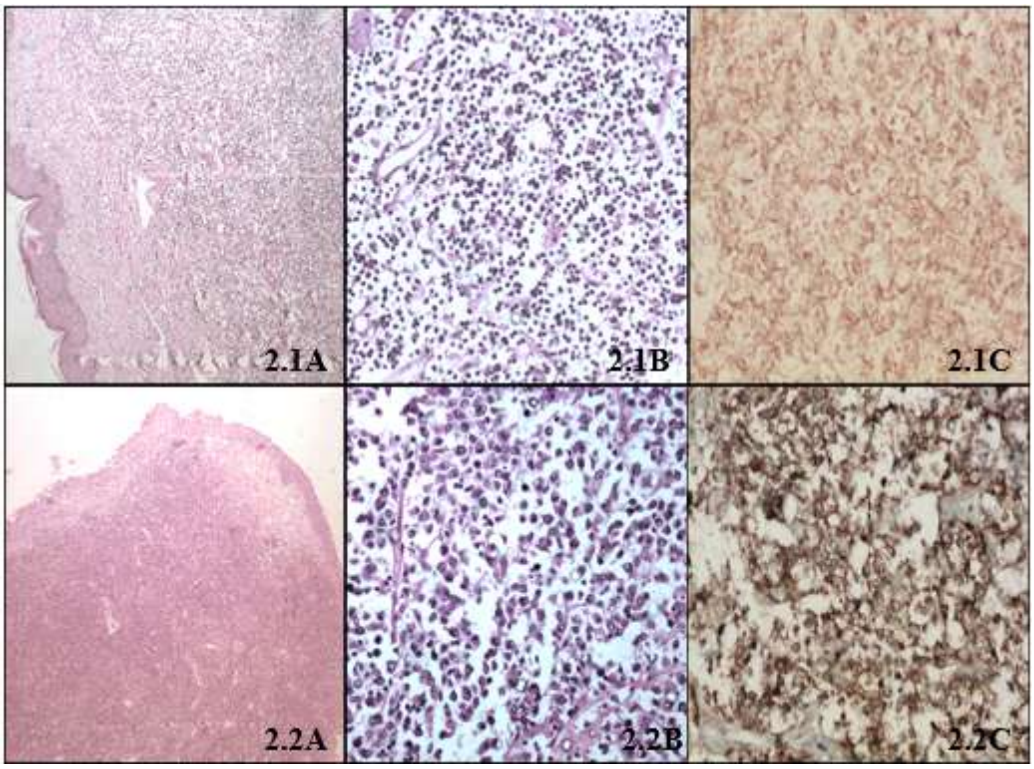

Fig 2.1 Primary cutaneous follicle centre lymphoma (PCFCL). A- H&E (x100). B- H&E (x200). C- Positive staining with antibody CD20. Fig 2.2 Primary cutaneous diffuse large B-cell lymphoma, other (DLBCL). A- H&E (x100). B- H&E (x200) C- Positive staining with CD 20.

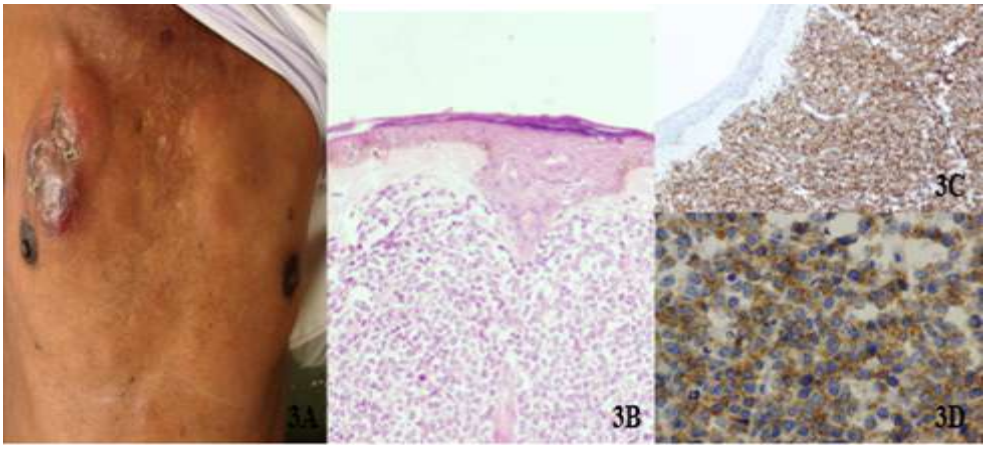

Fig 3 Blasticplasmacytoid dendritic cell neoplasm (BPDCN). A- Nodular lesion of BPDCN over chest wall. B- Monotonous blast like cells in the dermis with sparing of epidermis. C- CD56 positive neoplastic cells. D- CD123 positive neoplastic cells.

VI. Conclusion

Cutaneous lymphomas encompass a wide variety of lesions and our study is an attempt to evaluate the distribution and subtypes of cutaneous lymphomas, both primary and secondary in a regional cancer centre in South India. The frequency of primary and secondary involvement was similar to the study conducted in Korea. This probably does not reflect the true incidence in our population for various socioeconomic and geographic reasons and also because only a subset of patients are referred to a tertiary cancer centre for treatment.Secondary involvement by a systemic lymphoma should always be ruled out by proper staging before considering PCL. Although histological examination can give us a list of possibilities,immunophenotyping of cutaneous lymphomas is mandatory for accurate diagnosis which in turn has therapeutic and prognostic implications.

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