The T cell Predominance: Peripheral T cell Lymphoma-not Otherwise Specified

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Abstract
Peripheral T cell lymphomas (PTCL) as an uncommon disorder constitute an estimated 10% of non Hodgkin’s lymphoma. Current immune phenotypes and molecular signatures connote an estimated one third to one half (30% to 50%) instances of PTCL as “not further classifiable”. Peripheral T cell lymphoma arises in elderly individuals with a median at 60 years of age and a male predominance. Peripheral T cell lymphoma (PTCL) is predominantly categorized into nodal or extra-nodal configurations with cutaneous involvement or peripheral blood leukaemia. Medium or enlarged lymphoid cells with a clear cytoplasm are demonstrated with a T cell characterization of immune reactive CD3+, CD45RO+, CD2+, CD5+ and CD7+ and a germinal centre immune phenotype (CD10+, BCL6+, MUM1-). Genetic evaluation of PTCL NOS discerns recurrent genetic abnormalities of TET2, DNMT3A, IDH2 and RHOA genes. Bone marrow biopsy is a critical investigation for staging of lymphomas and assessment of abnormal haematological parameters. The therapeutic management of peripheral T cell lymphoma (PTCL) is identical to diffuse large B cell lymphoma (DLBCL) and utilizes combinations such as cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone (CHOP-EP) in individual’s ≤ 65 years of age and a combination of cyclophosphamide, doxorubicin, vincristine, prednison (CHOP) in patients ≥ 65 years of ages.

Preface
Peripheral T cell lymphomas (PTCL) as an uncommon disorder may constitute an estimated 10% of non Hodgkin’s lymphoma and 6% of combined lymphomas[4-6]. A peripheral T cell lymphoma- not otherwise specified (PTCL-NOS) as a frequent subset depicts an estimated 25% instances of peripheral T cell non Hodgkin’s lymphoma. The International T cell Lymphoma Project exemplifies a comparable emergence of the disorder within Europe (34.3%) and United States (34.4%) with a lesser incidence in Asia (22.4)[1,2]. An initial lymph node enlargement is accompanied by incrimination of hepatic, dermal or splenic viscera and the bone marrow in 22% instances. An advanced, progressive stage of preliminary disease(70%) appearance is common with at least two thirds of the individuals elucidating an intermediate to high international prognostic index (IPI)[3,4]. As per the contemporary world health organization (WHO) classification, a peripheral T cell lymphoma- not otherwise specified (PTCL-NOS) is a disease which is discordant with alternative forms of PTCL[4-5]. The current immune phenotypes and molecular signatures connote an estimated one third to one half (30% to 50%) instances of PTCL as “not further classifiable”[1,2].

Disease Characteristics
Peripheral T cell lymphoma usually arises in elderly individuals with a median at 60 years of age. A male predominance is elucidated with a male to female proportion of 2:2.5:1 (M: F: 9:4)[1,3]. Peripheral T cell lymphoma (PTCL) is predominantly categorized into nodal or extra-nodal configurations with cutaneous involvement or peripheral blood leukaemia, contingent to clinical representation and the implicated viscera[4-6]. Disease detection in peripheral T cell lymphoma is commonly delayed till the lymphoma disseminates to associated organs, particularly the bone marrow which generally indicates an advanced stage of disease. The disorder modifies normal haematopoietic mechanisms of the bone marrow. The therapeutic management of the lymphoma may be intricate. The infrequent disorder of peripheral T cell lymphoma is predominantly evaluated on clin-
Morphology and Immune Phenotype

The morphological variations concur with aggressive tumour subtypes. A follicular or a peri-follicular growth pattern with predominantly obliterated lymph node architecture is exhibited. Medium or enlarged lymphoid cells with a clear cytoplasm are demonstrated. In addition, the cytological elucidation is diverse, the cellular circumscription is of inflammatory or reactive lymphocytic cells and the diffuse tumour cell infiltrate is confined to the para-cortical zone.

The immune histochemical profile depicts a T cell characterization with immune reactive CD3+, CD45RO+, CD2+, CD5+ and CD7+. An immune reactive pan T cell marker is absent in the malignant cells, thus describing an aberrant immune phenotype. Majority of the instances depict a CD4+/CD8- mature T helper cell phenotype with the remaining one fifth (20%) instances displaying a CD4-/CD8+ immune reaction. The immune phenotypes of CD4-/CD8- or CD4+ /CD8+ are infrequently cogitated as the neoplasm is morphologically heterogeneous with a lack of characteristic features, the diagnosis is usually one of exclusion.

Molecular Characteristics

The molecular signature of PTCL demonstrates a clone specific genetic rearrangement of the x and β T cell receptor (TCR) with an estimated 10% instances depicting a clone specific genetic rearrangement of the immunoglobulin heavy (IGH) locus. Repetitive chromosomal translocations of t (5;9) (q33;q22) induce an ITK-SYK fusion. A germinal centre immune phenotype (CD10+, BCL6+, MUM-) and immune reactive CD4+ is delineated within the tumour cells. Chromosomal translocations such as the IRF4/MUM1 associated with T cell receptor alpha partner gene are exceptionally cogitated with the PTCL NOS variant. Gene expression profiling (GEP) varies with the heterogeneous morphology of the lymphoma. A concurrent Epstein Barr viral (EBV) infection is accompanied by an inferior prognosis. Molecular attributes depicted by the heterogeneous lymphoma are diverse. Gene expression profiling (GEP) additionally classifies PTCL into specific subtypes. An estimated 15% of the PTCL NOS are re-assigned as an angioimmunoblastic T cell lymphoma (AITL) whereas roughly 10% of anaplastic large cell lymphoma (ALCL) or extra-nodal NK/T cell lymphoma is excluded from PTCL NOS category. Genetic evaluation of PTCL NOS discerns certain recurrent genetic abnormalities of TET2, DNMT3A, IDH2, RHOA genes along with an immune reactive CD28+.

A T follicular helper (TFH) phenotype is elucidated with AITL. Follicular variant of PTCL NOS is re-categorized as a subtype of follicular helper cell lymphoma with the current world health organization (WHO) classification 2016. Repetitive genetic fusion of VAV1 encodes a critical constituent of T cell lymphoma receptor signalling, as detected in restricted instances of PTCL NOS and ALCL. Genetic remodelling of ITK genes such as SYK, FER and ERBB4 is concurrent. Genetic modifications control the cellular growth along with evolution of T cell lymphoma besides recognizing inherent therapeutic targets in specific clinical trials. Genetic rearrangements of TP63 consistently reoccur with lymphomas such as PTCL NOS and ALCL and characterize an enhanced cellular proliferation with an inferior prognosis. Categorical biological and prognostic subtypes are exemplified with the diverse PTCL NOS. Chief molecular signatures identifiable remain the type I with an amplified GATA3 and enriched genetic modifications concordant to cellular proliferation (such as the MYC gene) or a mammalian target of rapamycin and β catenin.

The associated type II preponderantly exhibits TBX21 (T bet) with genetic appropriations incited with interferon γ and NF-KB signalling mechanisms. The second subtype enunciates amplified genetic transcripts associated with cytotoxic T lymphocytes (possibly the cytotoxic variant). Delineation of GATA3 eliminates the genetic remodelling of TBX21 along with a converse genetic manifestation (TBX21 excluding GATA3) thus ensuring a definitive demarcation betwixt the dual subcategories. Exemplification of GATA3 may confer an inferior prognosis with a 5 year overall survival (OS) of 19%. Additionally, genetic exhibition of TBX21 depicts a superior outcome and a 5 year overall survival (OS) of 38%. Elucidation of CD30 antigen demonstrates varying prognostic results within the subtypes of PTCL. Immune reactive CD30+ PTCL NOS collates a marked down regulation of genes implicated in T cell maturation/mobilization with surface antigens CD28, CD52, CD69, along with the transcription factor NFATc2 and the T cell receptor signal transduction (tyrosine kinases Lck, Fyn, Itk). CD30+ PTCL NOS concomitantly manifest amplified transcription factors such as Jun B and MUM1/IRF4.

The morphological presentation and genetic enunciation of the admixed CD30+ PTCL NOS and the ALK- ALCL is identical with a superior overall survival (OS at 60%). In contrast, the non reactive CD30 - and reactive CD30+ forms of PTCL depict a contradictory pattern of genetic elucidation. Also, the immune non reactive CD30- PTCL NOS demonstrate diverse molecular manifestations apart from variable clinical expressions, an overall survival (OS) of 24 months and a progression free survival (PFS) of 10.5 months. However, the prognostic significance of CD30 elucidation is be currently obscure. PTCL NOS can be demarcated on account of manifested GATA3/TBX21 molecular modifications besides enunciation of CD30. Nevertheless, the clinical and diagnostic advancement does not impact the selection of first line therapeutic options.
Figure 1 PTCL: enlarged cells with lobulated nuclei\(^{17}\)

Figure 2 PTCL: venular prominence with plump endothelium and enlarged lymphocytic cells\(^{17}\)

Figure 3 PTCL: obliteration of lymphoid architecture and variable lymphoid follicles with germinal centres\(^{18}\)

Figure 4 PTCL: diffuse lymphoid infiltrate of enlarged cells with clear cytoplasm and vesicular nuclei\(^{19}\)

Figure 5 PTCL: intense cellular pleomorphism of giant lymphoid cells displaying vesicular nuclei with conspicuous nucleoli\(^{19}\)

Figure 6 PTCL: diffuse and patchy assembly of medium to enlarged atypical lymphoid cells with effaced lymphoid architecture\(^{17}\)

Figure 7 PTCL: dissemination of aberrant, enlarged lymphoid cells with focal nuclear hyperchromasia and paraprotein deposition\(^{20}\)

Figure 8 PTCL: mammoth lymphoid cells, vesicular nuclei with nuclear pleomorphism, anaplasia and conspicuous, multiple nucleoli\(^{21}\)
Figure 9 PTCLU: undefined and monomorphic dispersal of aberrant, enlarged lymphocytic cells

Figure 10: PTCL variable dissemination of variegated and giant lymphocytic cells with clear cytoplasm, vesicular nuclei and nucleolar prominence

Figure 11 PTCL: aggregates and clusters of loosely cohesive atypical, enlarged lymphocytic cells

Figure 12 PTCL: scattered, mammoth lymphocytic cells with nuclear dimorphism and binucleation, vesicular nuclei, significant nucleoli

Figure 13 PTCL: aberrant lymphocytic cells with immune reactive CD3+

Figure 14 PTCL: atypical, enlarged lymphocytic cells with immune reactive CD8+

Figure 15 PTCL: abnormal lymphocytic cells with immune reactive CD30+

Figure 16 PTCL: aberrant lymphocytic infiltrate with immune reactive CD5+
Investigative Profile
The complete blood count is anomalous with anaemia, thrombocytopenia, neutropenia and lymphocytosis on account of bone marrow replacement by the lymphoma. Myelodysplasia appears to be an adjunctive aetiology for anaemia and pancytopenia commonly exemplified within the elderly population[14,15]. A cytogenetic chromosomal evaluation with a fluorescent in situ hybridization (FISH) of the bone marrow often appears non-confirmatory for the lymphoma. CD4/CD8 immune phenotype of the peripheral T cell lymphoma concurs with atypical peripheral blood findings. Majority of the lymph nodes afflicted by PTCL NOS configure the T helper cell phenotype (CD4+ /CD8+)[16]. Lymphoma with a CD4+ /CD8- phenotype correlates with the occurrence of anaemia and thrombocytopenia. Neutropenia generally concurs with PTCL immune phenotype of CD4+ /CD8- and CD4+ /CD8+. Lymphocytosis usually appears with CD4+ /CD8+ T cell lymphoma phenotypes. CD4+ T cells are crucial for signal transmission of the immune system and bone marrow haematopoiesis[16,17]. Functional impairment of the CD4+ T cells modifies the normal haematopoiesis, particularly erythropoiesis and thrombopoiesis. Propagation of CD8+ T cells induces a peripheral blood lymphocytosis, especially with lymphoma of CD4+ /CD8+ phenotype. Bone marrow biopsy is a critical investigation for staging of lymphomas and assessing the abnormal haematological parameters. A peripheral T cell lymphoma confined to the bone marrow incites a pancytopenia with a reduction in overall survival (OS) and disease free survival (DFS). Peripheral T cell lymphoma tends to persist within areas of emergence or initial presentation. Peripheral T cell lymphoma requires competent therapies and appropriate supportive measures in order to enhance the prognostic determinants[15,16].

Radiographic Assay
Application of a positron emission computerized tomography (PET-CT) scan is beneficial for disease evaluation in order to obtain specific prognostic information and assessment of therapeutic response. Hepatic or pulmonary incrimination by the lymphoma is exemplified with an inferior prognosis. Currently, the conventional applicability of a PET scan for disease staging or restaging is not advocated[12]. Attributes of tumour progression detected on a positron emission tomography (PET –CT) scan at the termination of induction therapy can be evaluated. Indicators of disease progression as elucidated with a positive PET scan can be discerned in individuals following an autologous stem cell transplant (ASCT) and the features quantify a decline in the survival[13,15]. The manifestations are particularly discernible with patients of PTCL NOS and angioimmunoblastic T cell lymphoma (AITL). Investigating the lymphoma with a provisional or an interim PET scan during therapeutic induction appears to be debatable. An intervening, provisional PET scan with absent features of malignant transformation (as per an international harmonization project or a Deauville 5 point scale) depicts a favourable overall survival (OS) and a progression free survival (PFS). Patients with an equivocal or a negative PET scan are suitable candidates for a consolidation therapy and a superior overall survival (OS)[15,16].

Prognostic Indices
Numerous prognostic models are cogent in indicating the risk stratification of individuals detected with PTCL NOS[1]. The international prognostic index (IPI) as applicable for aggressive Non Hodgkin’s lymphoma can be validated for a T cell neoplasm. The IPI appropriately reflects superior therapeutic outcomes with minimal values such as a 0/1. The lesser values (0/1) with concomitant favourable prognosis delineate a 5 year failure free survival (FFS) of 36% and a 5 year overall survival (OS) of 50%. The greater prognostic score of 4/5 cогitates a 5 year overall survival (OS) of a mere 11% and a 5 year failure free survival (FFS) of 9%[11]. Contemporary models to predict survival outcomes in PTCL NOS incorporate the prognostic index for T cell lymphoma (PIT) and the modified prognostic index for T cell lymphoma (m PIT). The international prognostic index (IPI). model includes attributes such as age greater than 60 years, Eastern Cooperative Oncology Group (ECOG) performance status beyond 1 and elevated serum lactate dehydrogenase (LDH) values. The prognostic index for T cell lymphoma (PIT) further evaluates bone marrow infiltration. The modified prognostic index for T cell lymphoma (m PIT) additionally correlates manifestation of proliferation associated protein Ki67[1,5]. An alternate prognostic index obtained from the international T cell lymphoma project (ITCLP) incorporates aspects such as age greater than 60 years, Eastern Cooperative Oncology Group (ECOG) status beyond 1 and thrombocytopenia with the platelet count being below 150,000/ cubic millimetre, as the three critical parameters to appropriately categorize risk of disease progression and mortality of individuals with PTCL NOS[2,3]. The prognostic indices are authenticated with therapeutic regimens employing cyclophosphamide, doxorubicin, vincristine, prednimase (CHOP) or with anthracycline based regimens. Prognostic indices classify PTCL NOS into three (m PIT, ITCLP) or four (IPI , PIT) categories of disease outcome. Individuals calculated with a low risk delineate a superior prognosis, in contrast to alternative high risk categories[11,12]. An estimated two thirds (60%-70%) individuals demonstrate reoccurrence of disease within 5 years.

Therapeutic protocols
The traditional therapeutic management of peripheral T cell lymphoma (PTCL) is identical to diffuse large B cell lymphoma (DLBCL)[8,9]. Apart from the variant of ALK+ ALCCL, prognosis of the disease spectrum is unfavourable. Optimal therapy for approaching a patient with PTCL is currently inadequately defined, particularly in instances of residual disease[10,14].
Therapeutic procedures applicable for PTCL are:

**Induction therapy**
The defined protocol is employed from stage I to IV.
- The patient is subjected to appropriate clinical trials.
- The administration of combined cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone (CHOEP) is suitable for afflicted individual’s ≤ 65 years of age.
- The prevalent chemotherapeutic combination of cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) is pertinent for patient’s ≥ 65 years of age

**Initial Response**
- An autologous stem cell transplant can be indicated and beneficial.
- A consultation or appropriate investigations are a periodic pre-requisite at 3-4 months for duration of 2 years. Subsequently, an evaluation is necessitated at a 6 year intermission following initial diagnosis

**Interim Response**
- A complete or a partial therapeutic response can initiate the application of a comprehensive and contemporary therapy.
- The investigations depicting specific, disease oriented findings necessitate a repetition of the investigative assay.
- The residual or persistent disease mandates an additional histological assessment.
- The disorder elucidates a lack of therapeutic response or a progressive disease.

**Refractory or Relapsed PTCL**
- Patients depicting a refractory or a relapsed disease prove to be candidates for an augmented chemotherapeutic regimen.
- Contemporary regimen lacking a bilateral or multiple drug resistance incorporate combinations such as ifosfamide, carboplatin and etoposide (ICE), etoposide, methyl prednisolone, high dose cytarabine, cisplatin (ESHAP), gemcitabine and oxaliplatin (GemOx) or gemcitabine, dexamethasone, cisplatin, (GDP). Additionally, singular agents such as pralatrexate, brentuximab vedotin, romidepsin and belinostat may be beneficially employed
- Candidates which are unsuit for a chemotherapeutic augmentation are selected for clinical trials.
- Administration of chemotherapy with solitary agents such as pralatrexate, brentuximab vedotin, romidepsin, belinostat, gemcitabine and bendamustine may be advantageous.
- Individuals with a complete or a partial response often require an augmentation of chemotherapeutic protocols with a synergistic autologous stem cell transplant. The therapeutic modalities are cogitated as category 1 for refractory patients in complete remission and as category 2A for the remaining individuals
- An allogeneic stem cell transplant remains an advantageous option.
- Individuals depicting a lack of therapeutic response appear suitable for entering a clinical trial. An optimal, supportive care can be extended.
- Patients depicting a second relapse or an enhancement of disease severity or a disease progression can be adopted for a clinical trial. Adjunctively, lenalidomide is administered. Such candidates can additionally be managed with singular agents such as pralatrexate, brentuximab vedotin, romidepsin, belinostat, gemcitabine or bendamustine

**Table A: Incidence of Peripheral T cell Lymphoma**

<table>
<thead>
<tr>
<th>Category</th>
<th>Incidence (%)</th>
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<tbody>
<tr>
<td>Peripheral T cell lymphoma- not otherwise specified</td>
<td>25.9%</td>
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<tr>
<td>Angio-immunoblastic T cell lymphoma</td>
<td>18.5%</td>
</tr>
<tr>
<td>NK/T cell lymphoma</td>
<td>10.4%</td>
</tr>
<tr>
<td>Adult T cell leukaemia/lymphoma</td>
<td>9.6%</td>
</tr>
<tr>
<td>Anaplastic large cell lymphoma (ALK+)</td>
<td>6.6%</td>
</tr>
<tr>
<td>Anaplastic large cell lymphoma (ALK-)</td>
<td>5.5%</td>
</tr>
<tr>
<td>Enteropathy associated T cell lymphoma(type I)</td>
<td>4.7%</td>
</tr>
<tr>
<td>Primary cutaneous ALCL</td>
<td>1.7%</td>
</tr>
<tr>
<td>Hepatosplenic T cell lymphoma</td>
<td>1.4%</td>
</tr>
<tr>
<td>Subcutaneous panniculitis like T cell lymphoma</td>
<td>0.9%</td>
</tr>
<tr>
<td>Unclassifiable PTCL</td>
<td>2.5%</td>
</tr>
<tr>
<td>Adjunctive T cell disorders</td>
<td>1.8%</td>
</tr>
<tr>
<td>Adjunctive non T cell disorders</td>
<td>10.4%</td>
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</tbody>
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**Table B: Immune/Genetic classification of T cell Lymphomas**

<table>
<thead>
<tr>
<th>Immune/ Genetic Marker</th>
<th>Lymphoma Subtype</th>
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<tbody>
<tr>
<td>CD56, CD57, EBER(in situ hybridization)</td>
<td>Extra-nodal NK/T cell lymphoma</td>
</tr>
<tr>
<td>CD56, CD57, EBER(in situ hybridization)</td>
<td>T cell large granular lymphocytic lymphoma</td>
</tr>
<tr>
<td>Cytotoxic proteins(TIA-1, granzyme B, perforin)</td>
<td>T cell large granular lymphocytic lymphoma</td>
</tr>
<tr>
<td>Beta F1</td>
<td>Subcutaneous panniculitis like T cell lymphoma</td>
</tr>
<tr>
<td>TCR gamma/delta</td>
<td>Gamma/delta T cell lymphoma</td>
</tr>
<tr>
<td>CD10, BCL-6,PD1,CX-CL13</td>
<td>Angio-immunoblastic T cell lymphoma</td>
</tr>
<tr>
<td>CD30, CD15,ALK-1, EMA</td>
<td>Anaplastic T cell lymphoma</td>
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<tr>
<td>CD103</td>
<td>Enteropathy associated T cell lymphoma</td>
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<tr>
<td>CD1a,CD34, TdT</td>
<td>T cell lymphoblastic lymphoma</td>
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<tr>
<td>TCR-1, FOXP3,CD25</td>
<td>Tcell prolymphocytic leukemia</td>
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<tr>
<td>TCR-1, FOXP3,CD25</td>
<td>Adult T cell leukaemia/lymphoma</td>
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**Table C: Variable parameters employed with Prognostic indices**

<table>
<thead>
<tr>
<th>Age(&gt;60)</th>
<th>ECOG(&gt;1)</th>
<th>LDH(elevated)</th>
<th>Ann Arbor (stage III/IV)</th>
<th>Extra-nodal involvement (≥2 sites)</th>
<th>Bone marrow involvement</th>
<th>Platelet count (&lt;150,000/cmm)</th>
<th>Ki-67( ≥ 80%)</th>
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Table D: Prognostic index and relevant scores with PTCL-NOS$^{[1]}$

<table>
<thead>
<tr>
<th>Index</th>
<th>Grade</th>
<th>Numerical score</th>
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<tr>
<td>International Prognostic Index (IPI)</td>
<td>Low</td>
<td>0/1</td>
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<tr>
<td></td>
<td>Low-intermediate</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Intermediate-high</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>4/5</td>
</tr>
<tr>
<td>Prognostic index for T cell lymphoma (PIT)</td>
<td>Group 1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Group 2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Group 3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Group 4</td>
<td>3 &amp; 4</td>
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</tbody>
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18. Image 3 Courtesy: Academic Oup.
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