



FRONTLINE

A LYMPHOMA ROUNDS PUBLICATION

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Dr. Kristin Richardson presented at the Chicago Lymphoma Rounds meeting in 2018, with Dr. Sunita Nathan moderating the case.

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Frontline is a Lymphoma Research Foundation (LRF) publication that features selected case presentations from LRF's Lymphoma Rounds professional education program which provides a forum for local lymphoma healthcare professionals to meet on a regular basis to discuss actual lymphoma cases in a collaborative environment.

Lymphoma Rounds is currently held in seven U.S. cities with participation of over 45 academic and community centers.

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Gray Zone Lymphoma: Not So Gray?

Presenters

Kristin J. Richardson, MD, Rush University Medical Center
(Pathology) Yahya A. Al-Ghamdi, MBBS, Rush University Medical Center
(Moderator) Sunita Nathan, MD, Rush University Medical Center

At the Chicago Lymphoma Rounds on January 17, 2018, physicians from the Rush University Medical Center presented a case of gray zone lymphoma. Kristin J. Richardson, MD, presented the case, Yahya A. Al-Ghamdi, MBBS, reviewed the pathology, and Sunita Nathan, MD, moderated the session.

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Gray Zone Lymphoma: Not So Gray?

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Case Background

A 34-year-old male presented to a local hospital with neck swelling and was noted to have right supraclavicular lymphadenopathy. There were no B symptoms (i.e. no fever, chills, night sweats, or weight loss). He had an excellent performance status and worked as an engineer.

Diagnosis

A positron emission tomography (PET) scan was done and demonstrated diffuse lymphadenopathy (notable in the right supraclavicular, paratracheal, and mediastinal regions), with a 4 to 4.5 cm mediastinal mass, and splenomegaly. Neither the spleen nor bone marrow were FDG-avid.

Pathological evaluation of the biopsied right supraclavicular lymph node revealed classical Hodgkin lymphoma, nodular sclerosis type, EBV-negative, CD15+, CD30+, PAX5+ (weakly), and CD20- (Figure 1).

Standard treatment with adriamycin, bleomycin, vinblastine, and dacarbazine

(ABVD) followed. A PET scan performed after the second cycle demonstrated marked improvement in the supraclavicular node, but persistence of the mediastinal mass (Deauville score of 3 to 4). Two additional cycles of ABVD were administered. A PET scan performed following the fourth cycle showed continued persistence of the mediastinal mass. The patient was referred to the Rush University Medical Center for a second opinion.

Biopsy of the mediastinal mass was recommended and performed. Pathological study of the specimen revealed sheets of lymphoid cells with areas of necrosis, consistent with diffuse large B-cell lymphoma, CD20+, CD30+, PAX5+, CD15- (Figure 2).

Therefore, the biopsies of the supraclavicular node and the mediastinal mass revealed two distinct but closely related lymphomas.

Case Evolution

To treat the persistent mediastinal mass that showed CD30+ diffuse large B-cell lymphoma, following 4 cycles of ABVD, the patient received three cycles of salvage rituximab,

ifosfamide, carboplatin, etoposide (RICE) therapy. A PET scan after the third cycle revealed a decrease in the size of the mediastinal mass; however, the Deauville score remained at 4.

Multiple additional opinions were obtained, and ultimately the patient underwent excision of the remaining mediastinal mass. Pathological examination of the excised tissue showed only necrotic cells and no viable lymphoma cells. High-dose chemotherapy using rituximab, carmustine (BCNU), etoposide, Ara-C, and melphalan (R-BEAM) followed by autologous peripheral blood stem cell transplantation was performed. At day 60, a partial response was noted by PET scan with a Deauville score of 3 to 4.

Consolidative radiation to the mediastinum resulted in a follow-up Deauville score of 1 to 2.

Discussion

Gray zone lymphoma is defined as a B-cell lymphoma with features of both diffuse large B-cell lymphoma and Hodgkin lymphoma. It is thought to arise from a common precursor thymic B-cell that later transforms and falls along a spectrum between diffuse large B-cell lymphoma and Hodgkin lymphoma; hence, the

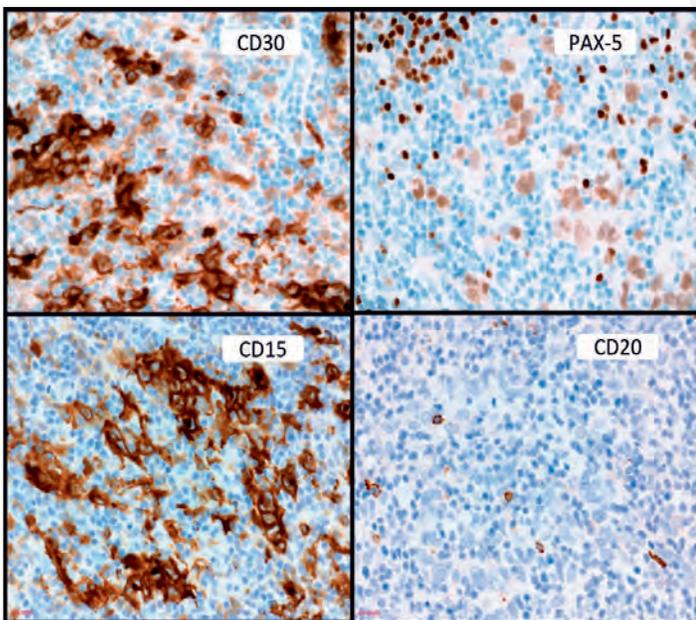


Figure 1. Biopsy of the patient's right supraclavicular lymph node.

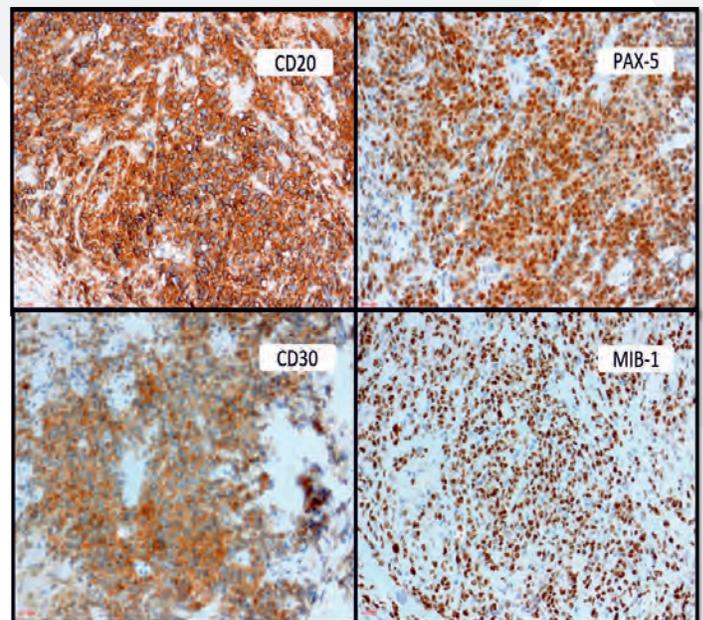


Figure 2. Biopsy of the patient's mediastinal mass.

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Gray Zone Lymphoma: Not So Gray?

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common term gray zone lymphoma. Although the World Health Organization classification includes the gray zone lymphoma as its own category, not all studies have confirmed it as a unique histological entity.

The diagnosis and treatment of gray zone lymphoma remains challenging. Given the rarity of this diagnosis and a paucity of prospective randomized trials, there is no clear standard of care for treatment of either the initial diagnosis or relapse of gray zone lymphoma. In general, clinicians are often guided by an initial biopsy result either toward a Hodgkin lymphoma or diffuse large B-cell lymphoma treatment regimen. A detailed review of all B-cell

markers with consideration of gray zone lymphoma when there is strong CD20 expression in otherwise classical Hodgkin lymphoma, or strong CD15 expression in primary mediastinal B-cell lymphoma, has been suggested as a strategy for diagnosis. Also consider a rebiopsy when Hodgkin lymphoma or diffuse large B-cell lymphoma does not respond to standard therapy for a possible alternative diagnosis of gray zone lymphoma.

Gray zone lymphoma has an aggressive course. While there are high rates of relapse, radiotherapy and autologous transplants have shown encouraging results for patients with refractory or relapsed disease. ■

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Multiply Relapsed Peripheral T-cell Lymphoma-NOS and Immunotherapy

Presenters

Parth Rao, MD
Icahn School of Medicine at Mount Sinai

(Pathology) Julie Teruya-Feldstein, MD
Icahn School of Medicine at Mount Sinai

(Moderator) Joshua Brody, MD
Icahn School of Medicine at Mount Sinai

At the New York Lymphoma Rounds meeting on January 24, 2018, physicians of the Icahn School of Medicine at Mount Sinai discussed a case of multiply relapsed peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) treated with immunotherapy. Parth Rao, MD, presented the case, Julie Teruya-Feldstein, MD reviewed the pathology, and Joshua Brody, MD moderated the session.

Case Background

A 66-year-old female was initially diagnosed in 2007 with stage III Hodgkin lymphoma and entered clinical remission following 6 cycles of standard treatment with adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD). PET scan showed no sign of disease at the completion of therapy. In January 2015, the patient presented with a 2- to 3-month history of an increasing neck mass and B symptoms, including weight loss and anorexia. An MRI study revealed extensive bilateral cervical, supraclavicular and mediastinal lymphadenopathy. PET scan confirmed bilateral hypermetabolic adenopathy. The patient has no other significant medical history. She is an active smoker.

Diagnosis

A lymph node biopsy was performed and the diagnosis of peripheral T-cell lymphoma-not otherwise specified (PTCL-NOS) was made at Icahn School of Medicine at Mount Sinai. Immunohistochemistry revealed

CD2+, CD3+, CD4+, CD5+, CD7-, CD8-, CD30- status and flow cytometry confirmed CD4+, CD7- expression.

Bendamustine treatment was administered over 6 cycles. At the end of treatment, PET scan revealed stable disease with a mixed response. The adenopathy in the neck and mediastinum was improved; however, a soft tissue density at the T12 vertebra was increased in size. The patient presented with new clinical evidence of disease progression, including back pain and axillary lymphadenopathy.

Case Evolution

The patient received radiation therapy administered to the symptomatic area and 2 cycles of ifosfamide, carboplatin, etoposide (ICE) salvage therapy. Following treatment, there was no evidence of disease.

Evaluation for autologous stem-cell transplant was interrupted due to delayed patient follow-up. PET scan revealed reappearance of adenopathy in the neck. Four additional salvage treatment cycles of ICE were administered. Repeat PET scan revealed no progression of disease after the fourth cycle of ICE.

Subsequently, progression of disease occurred and a repeat lymph node biopsy was performed. CD30+ status was demonstrated.

Given the CD30+ status, the patient was enrolled in a nivolumab/brentuximab vedotin clinical trial. Following 2 cycles of treatment, disease was determined by PET scan to be stable with a mixed response. The clinical trial was continued for 5 additional cycles with improvement in the neck adenopathy but a focal liver lesion and diffuse uptake in the pancreas was revealed by PET scan.

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In the 2017-2018 series, the Lymphoma Research Foundation issued nearly

700 Continuing Education certificates

from **21 activities** totalling

over **1,000 credit hours**

for healthcare professionals



Multiply Relapsed Peripheral T-cell Lymphoma-NOS and Immunotherapy

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Endoscopic ultrasound and fine needle aspiration of the pancreas was performed. Type 2 autoimmune pancreatitis was revealed, with no evidence for relapsed lymphoma or carcinoma. The patient complained only of occasional abdominal pain, but her lipase was markedly elevated (>1600 U/L) (Figure 1), liver function was normal and there was no evidence for gall stone disease. Nivolumab was held due to suspicion of it as the etiology of the pancreatitis, brentuximab vedotin monotherapy continued, and prednisone therapy initiated. The lipase levels and clinical symptoms temporarily improved, but the pancreatitis recurred after 2 cycles of brentuximab vedotin (Figure 2). PET scan revealed no evidence of disease in any location. Prednisone was resumed for treatment of pancreatitis, all other medications discontinued, and future treatment options were considered.

Discussion

Brentuximab vedotin has been shown to be highly active for treatment of CD30+ lymphoma, including relapsed disease, and to a lesser extent for refractory cases. Brentuximab vedotin has been associated with pancreatitis, usually presenting within the first 1 to 2 cycles of treatment. Nivolumab was associated with pancreatitis in 2% of patients with melanoma in a recent study.

Treatment of T-cell lymphoma that is refractory to standard therapies is a difficult problem without a clear consensus for treatment course. Salvage chemotherapy followed by stem cell transplant is one often preferred option but may not be tolerated or possible for patients with this disease status. The expected duration of clinical remission induced by novel agents, such as nivolumab and brentuximab vedotin, is unknown. Additional experimental therapies would be welcome, including chimeric antigen receptor (CAR) T-cell constructs directed at T-cell antigens. An open clinical trial of a CD7 non-fratricidal CART is underway. ■

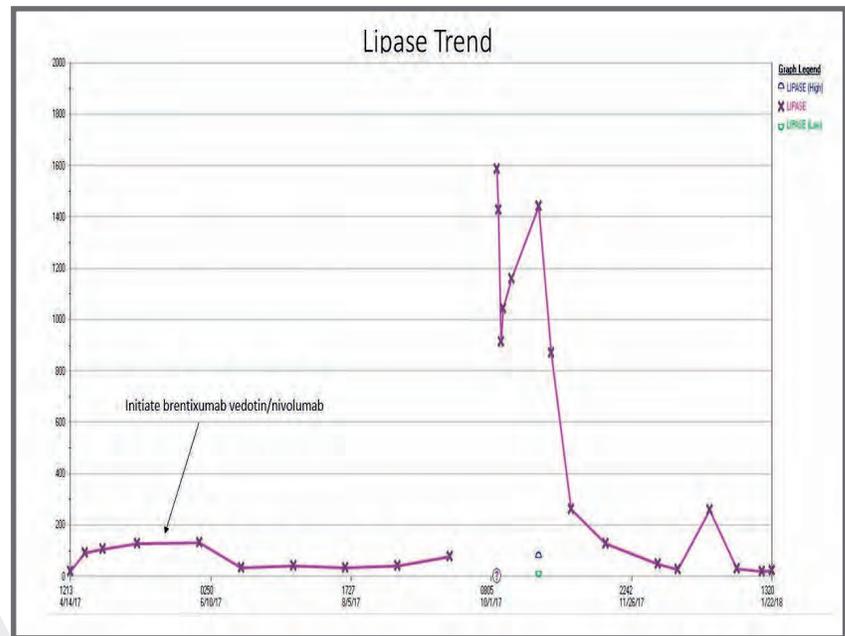


Figure 1: Patient with elevated lipase levels.

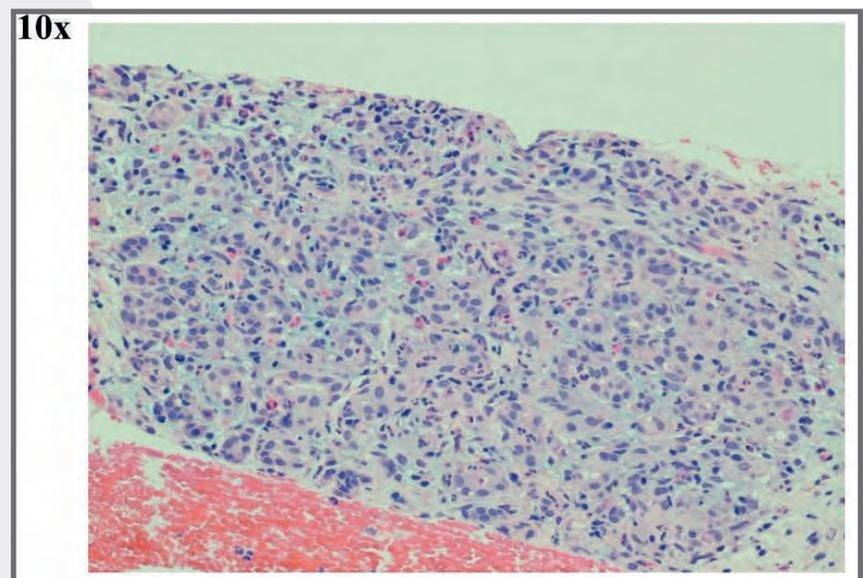


Figure 2: Patient developed pancreatitis after 2 cycles of brentuximab vedotin plus nivolumab.

Anti-CD19 CAR T-Cell Therapy in a Patient with Mantle Cell Lymphoma

Presenters

Samah Nassereddine, MD
George Washington University Cancer Center

(Moderators) Kieron Dunleavy, MD
Mitchell Smith, MD, PhD
George Washington University Cancer Center

At the inaugural Washington, DC Lymphoma Rounds meeting on April 4, 2018, physicians of the George Washington University Cancer Center discussed a case of relapsed/refractory mantle cell lymphoma (MCL) treated with a CD-19-directed chimeric antigen receptor (CAR) T-cell product. Samah Nassereddine, MD, presented the case and Kieron Dunleavy, MD, and Mitchell Smith, MD, PhD moderated the session.

Case Background

A 69-year-old male was initially diagnosed with MCL at the age of 58 years when he presented with fatigue, weight loss, and early satiety. Splenomegaly and diffuse lymphadenopathy were noted at that time. PET scan confirmed large hypermetabolic cervical lymph nodes, hilar lymphadenopathy, splenomegaly, and bone marrow involvement.

Diagnosis

The diagnosis of MCL was made following excisional biopsy of the right cervical lymph node. Immunohistochemistry revealed CD5+, CD19+, and cyclin D1+ status.

The patient enrolled in the ECOG E1405 clinical trial and received 6 cycles of R-hyper-CVAD, part A, with bortezomib. A complete remission was achieved at the end of treatment. He declined the protocol-directed maintenance rituximab because as an airline pilot he would have been unable to fly while on treatment.

Case Evolution

Four years later, the patient presented with symptomatic splenomegaly and diffuse lymphadenopathy. Bendamustine plus rituximab (B-R) therapy was administered as a second line of therapy over 6 cycles, followed by maintenance rituximab for 2 years. Complete remission was again achieved.

Four years after his second line of therapy, the patient presented with epistaxis, a nasal polyp, and cytopenia consistent with recurrent MCL with bone marrow involvement. The nasal polyp did contain MCL. Ibrutinib therapy was initiated with achievement of complete remission. However, 20 months later the patient developed massive splenomegaly, cytopenia,



Dr. Samah Nassereddine presenting at the Washington, DC Lymphoma Rounds meeting, April 4, 2018.

and diffuse lymphadenopathy. Splenectomy was performed as a palliative measure to control the cytopenia. Histologic evaluation of the section of spleen demonstrated MCL with Ki-67 expression of 60%, indicating more aggressive disease.

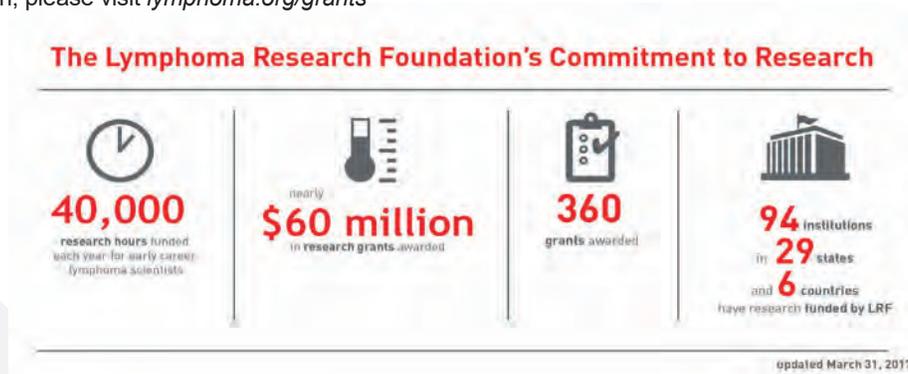
The patient was enrolled in the phase 2 ZUMA-2 trial, a multicenter study evaluating the efficacy of CD19-directed CAR T-cell product in subjects with relapsed/refractory MCL. Following a preparative regimen of fludarabine and cyclophosphamide, which was well tolerated, he received the CAR T-cell infusion in April 2017. His course was notable for febrile neutropenia without a source for infection, deemed a likely cytokine release syndrome; there was no evident neurological toxicity. Tocilizumab was not administered. To date, the patient remains in complete remission and experiences only mild fatigue and weakness. He walks 3 miles daily and exhibits no B symptoms. Laboratory studies are significant only for mild hypogammaglobulinemia. PET scan results reveal complete remission.

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Lymphoma Research Foundation Opens Applications for 2019 Young Investigator Grants

Applications for the Lymphoma Research Foundation's 2019 Young Investigator Grants are now open. These grants include the Postdoctoral Fellowship and Clinical Investigator Career Development Award, as well as the application for the Lymphoma Clinical Research Mentoring Program. Projects in all lymphomas and CLL are welcome in all three programs. The application deadline is **September 6, 2018**.

For more information, please visit lymphoma.org/grants



Anti-CD19 CAR T-Cell Therapy in a Patient with Mantle Cell Lymphoma

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Discussion

MCL, a rare form of non-Hodgkin lymphoma (NHL), comprises about 6% of NHL cases and typically occurs in males over the age of 60 years. Advanced stage of disease and B symptoms are common at presentation.

Diagnosis of MCL is made by histological evaluation of a tissue biopsy specimen with demonstration of characteristic B-cell immunophenotype, including CD5+ status and overexpression of cyclin D1. FISH analysis reveals a chromosomal translocation t(11;14) in 95% of cases. Complex cytogenetics, with acquired mutations that develop during the maturation process of the B-cells, can influence the clinical course and outcome. Cellular markers of proliferation, such as Ki-67, serve to predict disease course. For example, a Ki-67 of less than 10% suggests an indolent future progression, while Ki-67 greater than 30% is a poor prognostic feature which often is associated with blastoid/pleomorphic histology.

Chemotherapeutic regimens are highly efficacious for MCL; however, relapse is common. Several options for salvage therapy are approved and others are currently in phase 2 study. Ibrutinib treatment in a phase 2 study resulted in a 68% response rate, 17.5-month response time, 21% complete remission rate, and 13.9-month progression free survival time. Acquired resistance to ibrutinib is known, although the mechanisms are not fully understood, and portends compromised survival.

Treatment for asymptomatic patients with MCL remains controversial. Some advocate a conservative approach of delaying treatment until

symptoms or progression are evident, since treatment is not curative. The role of intensive therapy in the young, fit population also remains controversial. Current trials underway in the United States and worldwide should provide additional information regarding the optimal treatment course for MCL and efficacy of high-dose chemotherapy with stem cell support.

CAR-T-cell constructs targeting CD-19 are an efficacious and recently FDA-approved treatment option for relapsed/refractory B-cell lymphoma. This approach has been effective for individual patients with MCL and appears to be promising, but studies are in the early phases. The ZUMA-2 trial will provide additional information regarding the use of anti-CD19 CAR-T cell therapy for patients with refractory MCL (Figure 1). ■

Conclusions/Future Directions

- Anti-CD19 CAR T-Cell Therapy is highly effective in aggressive B-cell lymphoma
- Our patient with MCL continues in CR over a year after infusion of cells
- ZUMA2 will assess efficacy of this approach in MCL
- Challenges are overcoming neurological and cytokine release toxicities and addressing the cost of these approaches

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Figure 1: The use of CAR-T cell therapy is showing promise in patients with relapsed/refractory mantle cell lymphoma and clinical trials are ongoing.

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