Evaluation of Opportunities to Improve Hematopathology Diagnosis for Vietnam Pathologists

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ABSTRACT

Objectives: *We evaluate the need for, feasibility of, and impediments to improving hematopathology diagnoses for cancer hospitals in Vietnam.*

Methods: *Two hematopathologists from the United States visited three major cancer treatment hospitals in Vietnam to workshop a sampling of difficult hematopathology cases. With Vietnamese pathologists, they toured histopathology, immunohistochemistry, and ancillary laboratory facilities.*

Results: *Automated tissue processors and slide staining equipment were documented for each of the three hospitals. Between seven and 11 hematopathology cases were reviewed for each hospital. Exact/complete diagnostic concordance was 50% or less for all three laboratories. The major impediments to accurate specific diagnoses were limitations of immunohistochemical stains, limited stains available in house, and, for one of the hospitals, difficulty with interpretation of the immunohistochemistry.*

Conclusions: *Vietnamese pathologists would benefit from hematopathology training or opportunities to consult with hematopathologists in the United States. Expert hematopathology consultation services are currently unavailable within Vietnam, as postgraduate training for laboratory physicians consists of residency training in anatomic pathology only. Limitations in the quality of histopathology and immunohistochemistry could impose a barrier to success of efforts to improve hematopathology diagnosis. Implementation of a histopathology and immunohistochemistry quality improvement program might overcome this limitation.*

In his introduction to the 2016 update for the World Health Organization (WHO) classification of hematopoietic neoplasms, the associate editor for the journal *Blood* describes "remarkable progress" in the understanding and diagnosis of leukemias and lymphomas. Recent diagnostic innovations allow for improved options for therapies, including curative treatments for these diseases.[1] The revised diagnostic terminology allowing for more specific and directed therapies requires the pathologist and the laboratory to be responsible for correlation of clinical and morphologic findings and, in some cases, ancillary studies, including immunophenotyping, cytogenetics, and molecular diagnostic testing.[2,3] It has been predicted that cancer will increase as much as 70% by 2032, with most of these cases being in Asia, Central and South America, and Africa. Although patients in developing countries might benefit from new treatment protocols, it is not possible to effectively treat any malignancy without specific and accurate diagnoses. There is good evidence of underinvestment in both pathology education and laboratory development in low- and medium-income countries; this could be a barrier to diagnostic accuracy.[4] However, programs have overcome these barriers.[5]

Medical education for Vietnamese pathologists is similar to that in the United States, but it lacks opportunities for advanced or specialized training. Vietnamese high school graduates who have passed a basic science examination can be accepted to and attend a 6-year medical school. Postgraduate residency for pathologists consists of 3 years of training in anatomic pathology with

certification by a written examination, a written thesis, and an oral interview. There are no subspecialty training programs in Vietnam for lymph node pathology, bone marrow pathology, flow cytometric immunophenotyping, cytogenetics, or molecular diagnostics. Clinical laboratory training is typically part of a PhD program in laboratory science. There are no requirements for continuing medical education. This absence of structured training and experience in correlating hematopathology tissue histology, including bone marrow core biopsy specimens, with other clinical and laboratory findings led to a request by academic pathologists in Ho Chi Minh City, Vietnam (HCMC VN), for help from US pathologists.

In 2015, two American Board of Pathology–certified hematopathologists from the United States presented a single educational workshop on using the WHO 2008 classification system for hematopathology diagnosis in HCMC VN.[6] At the conclusion of the workshop, it was the impression and recommendation of the US pathologists that their Vietnamese counterparts would benefit from continued opportunities to review their cases with hematopathologists from the United States. When invited to return to Vietnam for follow-up workshops in 2016, the US hematopathologists sought to gather information needed to initiate the process of exploring such opportunities.

Materials and Methods

Public and private donors from the United States and Vietnam planned, funded, and organized site visits and workshops at what they believed were the three major academic oncology hospitals in the north and south of Vietnam. Prior to traveling to Vietnam, the US pathologists were sent diagnostic slides and clinical information to review from each Vietnam hospital for up to 11 patient cases considered challenging by the Vietnamese physicians. For some cases, paraffin tissue blocks were also sent, allowing the US pathologists to recut and restain as needed as well as to perform additional testing if deemed appropriate. Repeat immunohistochemistry was performed by Pensacola Pathologists Laboratory (Pensacola, FL), using an automated staining system with standard commercial reagents for immunostains (cyclin D1 and CD30) and Epstein Barr virus (EBER DNP) probes.

Upon arrival in Vietnam, the team of US pathologists was permitted to tour all areas of each of the three hospital laboratories and to collect data such as photographs and documentation of laboratory equipment, procedures, and protocols.

At each site visit, the workshop was introduced with a lecture detailing the 2016 updates to the WHO classification of lymphomas. Algorithms for lymphoma subclassification, beginning with microscopic morphology and incorporating ancillary studies including immunohistochemistry, were presented.[1,2] The cases submitted by each hospital were shown in lecture format at the submitting hospital, with that site's pathologists, clinicians, trainees, and students in attendance. For each case, photomicrographs of H&E-stained and immunostained sections provided by the institution were projected with a detailed discussion of the differential diagnosis and recommended algorithms for selection of immunostains and other ancillary studies. Each case presentation concluded with the preferred diagnosis of the US-trained hematopathologists supplemented, when available, by photomicrographs of immunostained sections prepared by a US laboratory. When time permitted, the US pathologists also reviewed current cases at each laboratory with that institution's pathologists and trainees.

Results

Existing equipment for the three hospital laboratories is listed in **Table 1**. All have automated systems for tissue fixation and routine staining. Two of the hospitals have automated equipment for performing immunoperoxidase stains. One has in-house capability for flow cytometric immunophenotyping. One has equipment and procedures for in-house molecular diagnostic testing. One has the equipment for scanning tissue-mounted glass slides, but it was observed that this piece of equipment was not operational at the time of the visit.

Comparison of Vietnam vs US tissue diagnoses is summarized in **Table 2** and detailed in **Table 3**, **Table 4**, and **Table 5**. Complete diagnostic agreement was observed in less than half of the cases, with most of both major and minor discrepancies attributable to limitations in the quality of slide preparation and immunostains. Decision making regarding algorithms for assessing and addressing immunostain failure became a part of the discussion at each site. An example of improved diagnostic accuracy aided by repeat immunostaining is illustrated in **Image 1**.

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Table 1
Existing Laboratory Equipment at Three Selected Vietnam Hospitals

Hospital	Tissue Processor	Routine Slide Stainer(s)	Immunohistochemistry Stainer(s)	Flow Cytometric Immunophenotyping	Molecular Diagnostics	Digital Slide Scanner
Ho Chi Minh City Vietnam Oncology Hospital	Automated on site	Automated on site	Automated on site	Sent to Ho Chi Minh City Blood Transfusion Hospital	Sent to Ho Chi Minh City Blood Transfusion Hospital	On site
Hanoi Vietnam K Hospital	Automated on site	Automated on site	Automated on site	Not available (possible future acquisition?)	In house	Budgeted; requesting recommendations
Hanoi Vietnam National Institute of Hematology and Blood Transfusion	Automated on site	Automated on site	Manual staining	Six-color on site and four-color on site (turnaround time issues with interpretive reporting)	In house (molecular diagnostic and karyotyping laboratories)	Budgeted; requesting recommendations

Table 2
Concordance of Diagnoses Between US and Vietnam Pathologists

Hospital	Total No. of Cases Reviewed for Presentation	No. of Cases With Complete Diagnostic Agreement	No. of Cases With Partial Agreement	No. of Cases With No Agreement	Diagnostic Limitations	Comments
First hospital visited	8	2	3	3	Immunohistochemistry suboptimal in five of eight cases	Immunostains worked well for only one case where there was complete diagnostic agreement; for two cases where stains were repeated in United States, the repeat immunohistochemistry allowed for a specific diagnosis
Second hospital visited	11	4	4	3	Immunostains worked in six of the 11 cases but were misinterpreted for two cases and panel used was too limited for specific diagnosis in four cases	
Third hospital visited	7	2	1	4	Immunostains worked for all cases but diagnoses limited by limited panel of antibodies or difficulties with interpretation of the stain results	Some diagnostic discrepancies were explained by the Vietnamese pathologists as being due to long turnaround times for flow cytometric immunophenotyping results for correlation with immunohistochemistry, but the quality of histology and immunohistochemistry was sufficient for US pathologists to interpret; this is a hospital that would significantly benefit from ability to scan slides for review with US pathologists

Discussion

It is not possible to effectively treat cancer without specific and accurate diagnoses. The Vietnamese government health system has made cancer treatment protocols for leukemias and lymphomas resembling those used in the United States available to their patients, making it incumbent on their pathologists to optimize their diagnostic accuracy to the level of developed countries.

It was our observation that barriers to diagnostic accuracy for the limited number of leukemia and lymphoma cases reviewed for this report include suboptimal tissue processing and staining. A possible

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Table 3
Details of US and Vietnamese Pathologists' Diagnoses for First Hospital Visited

Case No.	Tissue	Vietnam Pathologist Diagnosis	Immunostains Performed in Vietnam
1	Lymph node	B-cell lymphoma, unclassifiable	CD3, CD5, CD10, CD20, CD23, BCL2, CD79a, BCL-6, Ki-67, cyclin D, TdT
2	Lymph node	Suspect mantle cell lymphoma	CD3, CD20, CD5, Ki-67, cyclin D1
3	Lymph node	Focal nodal diffuse large B-cell lymphoma	CD3, CD5, CD20, cyclin D1, CD10, BCL-6, Ki-67, MUM1, BCL-2
4	Lymph node	T-cell lymphoma vs reactive hyperplasia	CD20, CD10, BCL-2, BCL-6, cyclin D1, MUM1, CD3, CD5, Ki-67
5	Lymph node	Suspect angioimmunoblastic T-cell lymphoma	CD3, CD5, CD20, CD10, BCL-2, BCL-6
6	Thyroid nodule	Suspect histiocytic neoplasm	CK, EMA, LCA, CD3, CD20, CD15, CD30, CD56, ALK, vimentin, CD1a, S-100, CD68
7	Lymph node	Classical Hodgkin lymphoma	CD3, CD20, BCL-2, BCL-6, CD15, CD30, EMA, CD10
8	Skin	Cutaneous T-cell lymphoma	CD2, CD3, CD20, CD30, ALK

EBER-ish, in situ hybridization for Epstein-Barr virus.

Table 4
Details of US and Vietnamese Pathologists' Diagnoses for Second Hospital Visited

Case No.	Tissue	Vietnam Pathologist Diagnosis	Immunostains Performed in Vietnam
1	Lymph node	Mantle cell lymphoma	CD20, CD79, CD5, cyclin D1, BCL-2, CD10, BCL-6, CD23, CD3, TdT, CD99
2	Lymph node	Suspect follicular lymphoma	CD79a, CD5, CD10, BCL-2, BCL-6, cytokeratin
3	Lymph node	T-cell–rich, histiocyte-rich B-cell large cell lymphoma	CD20, CD79a, CD10, CD3, CD43, cyclin D1
4	Pleural fluid	Suspect T-cell lymphoma	CD20, CD79a, CD3, CD5, CD10, CD23, Ki-67
5	Lymph node	Suspect classical Hodgkin lymphoma	CD20, CD79a, CD10, CD3, CD5, CD15, CD30
6	Lymph node	Suspect classical Hodgkin lymphoma	CD30, CD15, CD3, ALK, EMA, CD79a, CD20
7	Abdominal mass	Primary peritoneal myeloid sarcoma	CD43, CD68, CD117, MPO+ BCL-2, Ki-67, CD19, CD20, CD79a, CD10, BCL-6, CD23, cyclin D1, CD3, CD5, CD56, cytokeratin, NSE, synaptophysin, CD34
8	Soft tissue mass, thigh	Myeloid sarcoma	LCA, CD34, CD117, CD43, CD99, CD56, CD2, CD3, CD5, CD7, CD10, CD15, CD19, CD20, TdT, MPO, myogenin, HMB-45, S-100
9	Nasopharynx	Suspect T-cell lymphoma	Cytokeratin, CD43, CD3, CD5, CD20, CD79a, CD56
10	Inguinal lymph node	Suspect T-cell lymphoma	CD20, CD79a, LCA, CD45RO, CD3, CD56
11	Lymph node	Suspect hematopoietic malignancy	CK, S-100, MelanA, HMB45, LCA, CD20, CD79a, CD19, CD3, CD7, CD34, CD68, CD21, CD23

EBER-ish, in situ hybridization for Epstein-Barr virus; NK, natural killer.

Additional or Repeat Immunostains Performed in United States	US Pathologist Diagnosis	Explanation for Diagnosis Discrepancy
MYC	Burkitt lymphoma	Suboptimal immunohistochemistry performed by Vietnam hospital
CD5, cyclin D1	Mantle cell lymphoma	CD5 and cyclin D1 immunostains performed in Vietnam nondiagnostic
CD10, BCL-2, BCL-6	Reactive lymph node hyperplasia	Suboptimal tissue fixation and sectioning with nondiagnostic immunostaining for CD10, BCL-2, and BCL-6 performed by Vietnam laboratory
	Suspect angioimmunoblastic T-cell lymphoma	Nondiagnostic immunostaining and EBER-ish not available at Vietnam laboratory; tissue not available for repeat staining by US laboratory
	Suspect angioimmunoblastic T-cell lymphoma	Nondiagnostic immunostaining and EBER-ish not available at Vietnam laboratory; tissue not available for repeat staining by US laboratory
	Suspect poorly differentiated carcinoma	Suboptimal tissue fixation and sectioning with nondiagnostic immunostains performed by Vietnam laboratory; tissue not available for repeat staining by US laboratory
	Classical Hodgkin lymphoma	No discrepancy
CD30	ALK-negative anaplastic large cell lymphoma	Suboptimal tissue fixation and sectioning with nondiagnostic immunostain for CD30 performed by Vietnam laboratory

Additional or Repeat Immunostains Performed in United States	US Pathologist Diagnosis	Explanation for Discrepancy
	Mantle cell lymphoma	No discrepancy
	Follicular lymphoma grades 1-2	Minor discrepancy; US pathologists having more experience with grading follicular lymphoma
	Diffuse large B-cell lymphoma	Minor discrepancy; US pathologists having more experience with classifying follicular lymphoma
	Probable metastatic disease but cannot exclude primary effusion lymphoma	High background- positive staining of CD3+ small T lymphocytes in cell block sections; insufficient stains for specific diagnosis
CD30, PAX-5	Classical Hodgkin lymphoma, mixed cellularity type	Diagnostic immunostains repeated by US laboratory
CD15	Classical Hodgkin lymphoma, nodular sclerosis type	Diagnostic immunostain repeated by US laboratory
	Primary peritoneal myeloid sarcoma	No discrepancy
	Myeloid sarcoma	No discrepancy
CD7, CD56	Extranodal NK/T-cell lymphoma, nasal type	Diagnostic stains performed by US laboratory
EBER-ish, CD4, CD8	Extranodal NK/T-cell lymphoma, nasal type, extranasal	All diagnostic stains not available at this Vietnam institution
	Suspect metastatic carcinoma	Limited panel of immunostains performed by Vietnam hospital; tissue block not available to US laboratory

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Table 5
Details of US and Vietnamese Pathologists' Diagnoses for Third Hospital Visited

Case No.	Tissue	Vietnam Pathologist Diagnosis	Immunostains Performed in Vietnam
1	Lymph node	Diffuse large B-cell lymphoma	LCA, CD20, CD79a, BCL2, MUM-1, CD10, BCL6, MYC, CD3, CD5, CD43, CD56
2	Lymph node	T-cell–rich, histiocyte-rich diffuse large B-cell lymphoma	LCA, CD20, PAX5, BCL2, BCL6, CD5, CD10, CD23, CD138, CD3, CD43, CD56, CD15, CD30, CD25, CD68
3	Nasal mass	Lymphoplasmacytic lymphoma	LCA, CD20, CD38, CD138, MUM-1, CD3, CD56, CD79a, CD5, CD10, CD23, cyclin D1
4	Lymph node	Castleman disease	CD3, CD5, CD10, CD20, CD23, CD68, BCL-2, MUM-1, BCL-6
5	Lymph node	Rosai-Dorfman syndrome	CD68, CD136, CD1a, CD3, CD5, CD20, CD10, BCL2, BCL6, CD30, CD56, cyclin D1
6	Large intestine	T-cell lymphoma	CD3, CD4, CD8, CD5, CD7, CD20, CD30, ALK-1
7	Lymph node	B-cell lymphoma with features intermediate between classical Hodgkin lymphoma and diffuse large B-cell lymphoma	LCA, CD20, CD30, BCL-2, MUM-1, EBV, CD3, CD43, CD79a, CD15, CD10, BCL6, MYC, ALK-1

EBER-ish, in situ hybridization for Epstein-Barr virus; HHV-8, human herpesvirus 8.

explanation for this deficiency could be the absence of uniform national standards in that country for histotechnology education and certification, as well as a lack of uniform standards for laboratory accreditation and quality. High school graduates can train to become histotechnologists in Vietnam by working for 4 years under a senior histotechnologist in a hospital laboratory. They can then become certified with a written examination. There are no continuing education requirements for Vietnamese histotechnologists and no formal training or certification opportunities in country for immunohistochemistry. Issues similar to those described here have been addressed in other resource-limited countries by providing in-country workshops and technical assistance provided by credentialed laboratory professionals.[7]

A lesser but observable limitation to diagnostic accuracy was lack of experience by the Vietnamese pathologists in handling complex correlations of clinical, morphologic, and laboratory information required for many hematopathology diagnoses, particularly in the setting of less than adequate histology. Vietnam's pathology residency training is limited to anatomic pathology. No opportunities for subspecialty training in hematopathology are available in Vietnam, and there are no requirements for continuing medical education. The option of postgraduate medical education in the United States for Vietnamese physicians presents language, academic, financial, and political obstacles. If training a core group of Vietnamese hematopathologists in accredited US programs is not feasible, other options need to be considered.

A program of hematopathology training workshops similar to the one described in this article could bring hematopathology education to Vietnam. Although diagnostic algorithms based on the 2016 WHO classification of hematopoietic neoplasms were part of the educational workshops presented at each institution in this report, there are no ongoing hematopathology educational opportunities in Vietnam or expert consultation service to reinforce such case-based learning. Consistent workshops similar to those described here could be the basis for future Vietnam hematopathology education and diagnostic quality improvement. This option would require a significant time and travel commitment on the part of trained expert laboratory physicians from the United States or other developed countries. There are financial and logistical barriers to organizing a regular schedule of workshops. Lack of a national requirement for continuing education for Vietnamese laboratory physicians might limit funding and attendance.

Recent publications in the medical literature have described telemedicine programs for cancer diagnosis in sub-Saharan Africa, despite the fact that specific treatment protocols are not available in those regions.[8] Innovations in digital imaging technology have provided an opportunity for pathologists in the United

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Additional or Repeat Immunostains Performed in United States	US Pathologist Diagnosis	Explanation for Discrepancy
	Diffuse large B-cell lymphoma	No discrepancy
	T-cell–rich, histiocyte-rich diffuse large B-cell lymphoma	No discrepancy
	Plasmacytoma	Limited exposure to this pathology/differential diagnosis for Vietnam diagnostic practitioners; tissue not available for staining in United States
	Reactive paracortical hyperplasia	Nondiagnostic immunostaining; HHV-8 and EBER-ish not available at this Vietnam hospital lab; tissue not available for repeat staining by US laboratory
	Suspect metastatic carcinoma	Nondiagnostic immunostaining performed by Vietnam laboratory; tissue not available for repeat staining by US laboratory
	Suspect granulocytic sarcoma	Limited immunostaining performed by Vietnam laboratory; tissue not available for repeat staining by US laboratory
	Classical Hodgkin lymphoma, mixed cellularity type	Suboptimal immunostaining performed by Vietnam laboratory; tissue not available for repeat staining by US laboratory

States to assist their resource-limited colleagues by using telemedicine. In addition to the advantage of scanned pathology slides with interpretive software allowing for real-time expert consultation, a database of digital scans of hematopathology cases could be used for future education and research. Notably, this option requires capital investment in slide-scanning equipment, interpretive software, consistently accessible internet, and a dedicated server with the capacity to store large files. There must be a willingness on the part of US pathologists to incorporate ongoing real-time telepathology into their consultation service. Implementation of slide-scanning technology and file transfer would require a trained laboratory informatics specialist to visit each of the target hospitals to assess technology, infrastructure, and the capacity for troubleshooting technical issues as they arise. Language barriers could create an obstacle to clear communication of accurate diagnoses. Investment of financial, human, and infrastructure resources has been made in Vietnam for facilitation of telemedicine diagnosis in other areas of medicine but not, as yet, in diagnostic pathology.[9]

Conclusions

Vietnamese pathologists would benefit from an opportunity to improve quality and consistency of hematopathology diagnoses at cancer hospitals in their country. Options for improved hematopathology education for Vietnam pathologists might include a continuing program of in-country workshops provided by US hematopathologists. A telepathology program would allow for more frequent access to US experience and expertise than periodic workshops. Limitations in the quality of histopathology and immunohistochemistry could impose a significant barrier to success of such programs. These limitations could be overcome by providing in-country histopathology and immunohistochemistry training by US volunteers. A continued program of regular hematopathology workshop presentations in major Vietnam cities would be beneficial. Such workshops require financial and logistical support in addition to committed hematopathologists willing to travel regularly to Vietnam. Telepathology could bring together US and Vietnam pathologists without such logistical and travel burdens. Notably, there are numerous obstacles to successful implementation of a telepathology program, including, but not limited to, the investment required for purchase or leasing of slide-scanning equipment along with purchase or solicitation of donating interpretive software, the work of skilled informatics and technology professionals, and computer servers required for this strategy. If these obstacles could be overcome, telemedicine between US and Vietnam pathologists could provide an opportunity for education, research, and quality improvement for cancer diagnoses in both countries.

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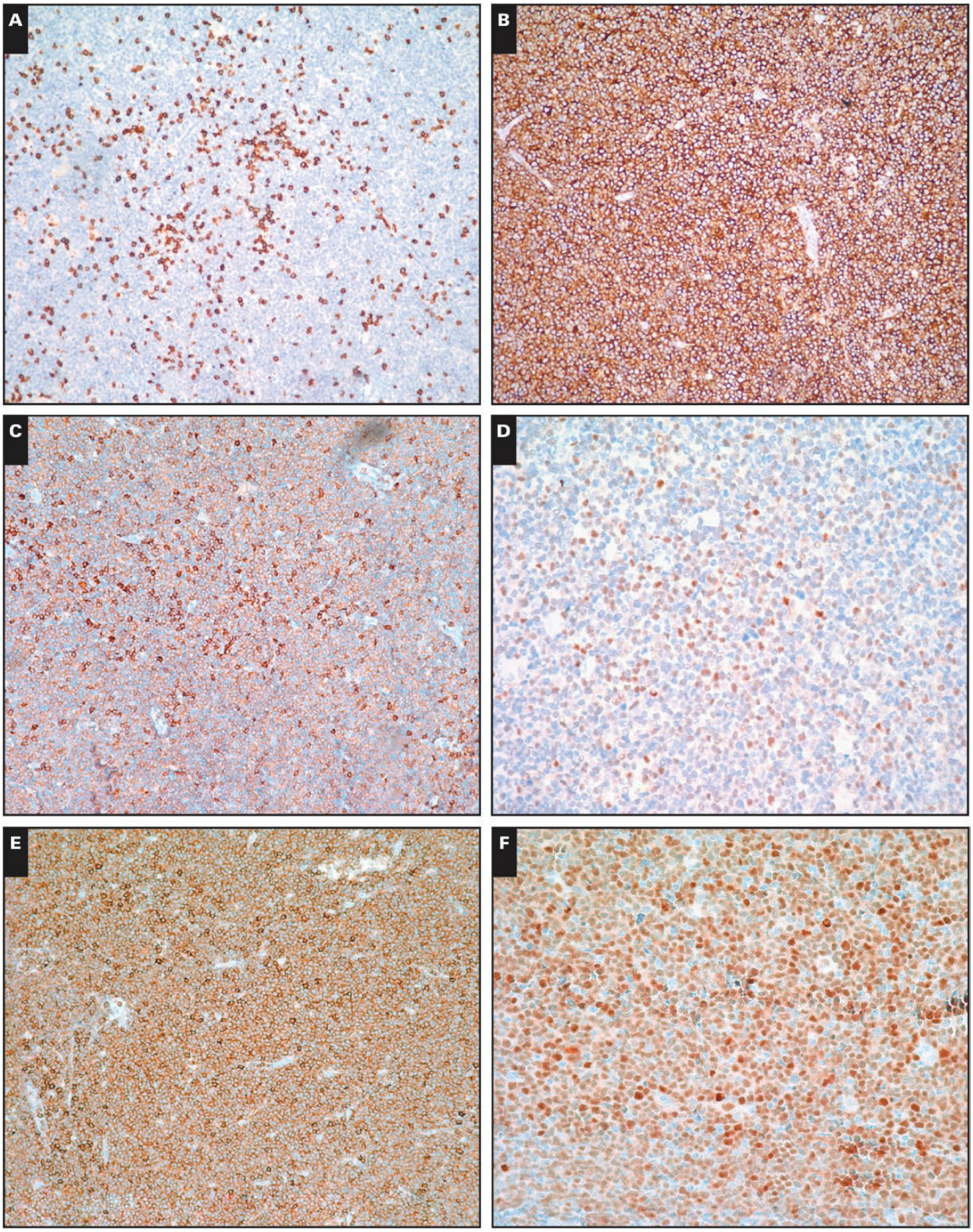

Image 1 Mantle cell lymphoma diagnosis aided by repeat immunoperoxidase staining performed in the United States. **A**, CD3 performed by Vietnam laboratory. **B**, CD20 performed by Vietnam laboratory. **C**, CD5 performed by Vietnam laboratory. **D**, Cyclin D1 performed by Vietnam laboratory. **E**, CD5 repeated by US laboratory. **F**, Cyclin D1 repeated by US laboratory.

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