Welcome from the

EDITOR

We are happy to share with you the second edition of GAPNews.

In this edition, Dr. Krishnamurti and Dr. Monsrud thoroughly discuss what is PD-L1 and its clinical applications and interpretation. They describe its role in cellular interactions and immunity, how it functions and its role in tolerance to tumors. They also provide us with a great summary on when to order the immunohistochemical stain and how to report the results.

Dr. Sikora from Grady health system updates us on the use of convalescent serum for the treatment of COVID19 patients.

We are also proud to share with you a few successes that Georgia pathologists were able to achieve on the legislative front.

Also in this edition, we hope you will enjoy an interesting case presentation by Dr. Shi, Dr. Ogunbona and Dr. Lubin on a biopsy from a tongue lesion from a 50 year old male.

We are proud to launch for the first time a “Member Spotlight” column. Our first Member Spotlight is Dr. Patrick Godbey, who is the current president of the College of American Pathologist and a Board Member of the Georgia Association of Pathology. Dr. Godbey was interviewed by Dr. Krishnamurti and Dr. Anderson.

We want to encourage you to get involved: we would love to hear from you! If you have an interesting case you would like to share or a colleague you believe we should spotlight; please reach out. We are happy to share the news of achievements and expansions within your laboratories, as well as advertise for job openings.

Please reach out to lara.harik@emory.edu, with any comments/suggestions or news you would like to share with members of the Georgia Association of Pathology and neighboring states.

Lara Harik, MD
Genitourinary Pathologist and Researcher
Emory University School of Medicine
Chair of the Education Committee and Board Member
Georgia Association of Pathology

Legislative
UPDATE

GAP officers working with the CAP and the MAG helped get two pieces of legislation across the finish line that are wins for Georgia pathologists.

On July 17, 2020 Governor Kemp signed two pieces of legislation that affect Georgia pathologists:

HB 888 - Reduction of Surprise Medical Billing: HB 888 is a bi-partisan reform that puts patients ahead of the status quo and provides a fair process for billing that medical providers and insurers can agree on when dealing with out of network services. By participating in a MAG established Out of Network Physician Coalition, GAP officers and their CAP partners were able to influence this legislation and insert language to protect pathologist interests. We believe the end result was fair and in some ways superior to what has passed in other states.

HB 789 – Network adequacy disclosure: Allows creation of a surprise bill rating system based upon the number of certain physician specialty groups contracted with a hospital within a health insurer's network. The bill compels health plans to disclose to consumers whether they had contracted with various specialty physicians at in-network hospitals. Plans that fail to indicate contracts with specialty physicians would be given a lower rating that consumers could rely upon when selecting their insurance provider.

The GAP officers want to thank you for your membership. We believe that an active state society (GAP) was very helpful in allowing us to positively influence legislation that affects Georgia pathologists.

CASE PRESENTATION

Presented by

Oluwaseun Ogunbona, MD
Pathology Resident

Dan Lubin, MD
Assistant Professor of Pathology

Judy Shi, MD
Lead author, Assistant Professor of Pathology, Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, GA

Multiple-choice question:

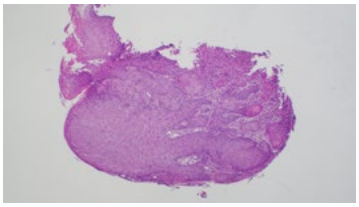
A 50-year old man presents with a tongue lesion which was biopsied (see images below). Which of the following is true regarding this lesion?

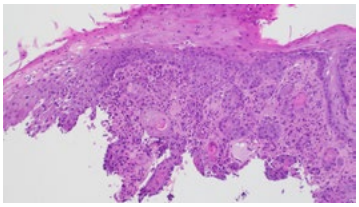
A. The tumor is a result of proliferation of all elements of peripheral nerves.

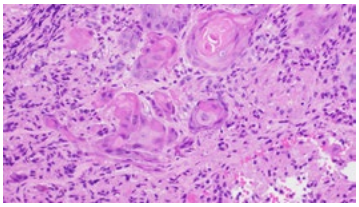
B. The tumor cells are filled with PAS+, diastase resistant granules.

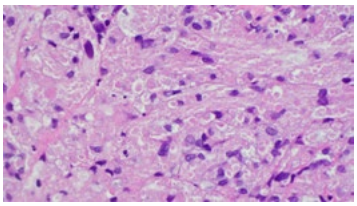
C. The associated epidermal process is characteristically found in basal cell carcinoma.

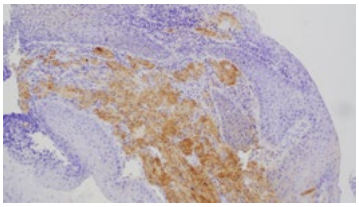
D. Leukoplakia and erythroplakia are precursors for this lesion.











See page 9 for the correct answer.

All You Need to Know on PD-L1
(Programmed Death Ligand-1)

Authors:

Ashley Monsrud, MD
Pathology Resident

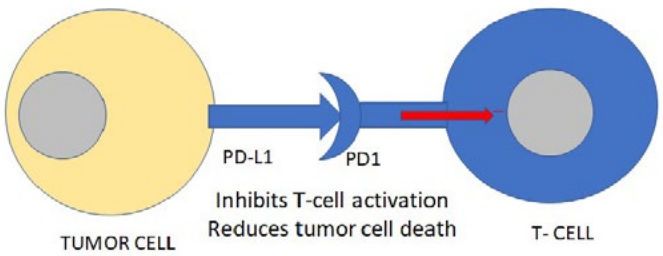
Uma Krishnamurti, MD PhD
Associate Professor of Pathology, Director of Surgical Pathology, Grady Healthcare System, Emory University School of Medicine, Atlanta, GA

Introduction

It is commonly known amongst physicians that PD-L1 (Programmed Death Ligand) inhibitors are used to treat various types of cancer. What exactly is PD-L1? What is its physiologic function and role in oncology? In this article we will discuss these questions, as well as treatment targeting PD-1/PD-L1, and laboratory testing to select cases eligible for PD-1/PD-L1 targeted therapy.

PD-1/PD-L1 interaction [1,2]

PD-1/PD-L1 are basic immune checkpoints in our body. Programmed cell death protein 1 (PD-1) is a receptor expressed on human immune cells (T cells, B cells). It is a binding ligand, the Programmed Death Ligand-1 (PD-L1), also known as B7-H1, is a 40kD type 1 transmembrane protein member of B7 family within the immunoglobulin receptor superfamily. PD-L1 that is present on antigen presenting cells, such as activated T cells, B cells, and macrophages, modulates T-cell mediated immune response. Presentation of an antigen on APC to T-cells, without PD-L1, results in activation of the T-cell response, and downstream clearance of the microorganism with the antigen that triggered an immune response. However, interaction of tumor cells or APC expressing PD-L1 with the PD-1 receptor on T-cells inhibits TCR-mediated activation of IL-2 production and T cell proliferation. Normal PD-1/PD-L1 interaction plays a role in immune tolerance and its absence is implicated in autoimmunity. PD-L1 expression by tumor cells helps them evade anti-tumor immunity. (Figure 1) PD-L2 is another PD-1 ligand but it's role in cancer progression and immune-tumor microenvironment regulation is not as well studied as the role of PD-L1.



The exact reason as to how tumor cells are able to express PD-L1 is still unclear, however, many studies propose that it has to do with the interaction and signaling between tumor cells and various cytokines i.e. IFN-g, IL-1a, IL-10 etc. Tumors can express PD-L1 innately or adaptively. Tumors can express PD-L1 innately/intrinsically through oncogenes. In glioblastomas, the deletion or silencing of phosphatase and tensin homolog (PTEN) drives PD-L1 expression through the PI3K-AKT cell signaling pathway. Various lymphomas and lung cancer can use the anaplastic lymphoma kinase (ALK) signaling pathway to upregulate STAT3 oncogenic pathway leading to PD-L1 expression. In Hodgkin's disease a gain of JAK2, PD-L1 and PD-L2 occur commonly through the gain of chromosome region 9p24. In an adaptive pathway, increased expression of PD-L1 on tumor cells is believed to be related to interferons (IFN) present in the tumor environment.

Effects of PD-L1 expression on tumors [3]

PD-L1 expression on tumors allows them to evade an anti-tumor immune response. Studies correlating tumor expression of PD-L1 expression with prognosis are ongoing. Several studies have shown that PD-L1 expression is associated with a poorer outcome, while some studies show that it has a better prognosis. In cancers such as renal cell carcinoma (RCC), non-small cell lung carcinoma (NSCLC), esophageal carcinoma, gastric carcinoma, and melanoma, PD-L1 expression is associated with poor prognosis. Meta-analysis of RCC showed that with a high expression of PD-L1 the risk of death increased by 81%. PD-L1 positivity in gastric carcinoma was found to be an independent prognostic factor and associated with a decreased survival time and higher stage. Statistically significant association with worse overall survival and poorly differentiated carcinoma was found in patients in NSCLC. Conflicting evidence on breast cancer and PD-L1 expression exist. A meta-analysis done by Guo et al. shows PD-L1 expression associated with higher nuclear grade, lymph node metastasis and increased 10-year mortality risk. On the contrary, another study shows that PD-L1 is a positive prognostic indicator with better overall survival in cases with PD-L1 expression. This is postulated to be due to the increased anti-tumor immune response present.

Treatment targeting PD-1/PD-L1 [2,4]

Blockade of PD-1/PD-L1 interaction can be achieved via three methods: (1) antibody blockade, (2) gene silencing, and (3) small-molecule pathway inhibition.

Currently, blockade using antibodies is the mode of therapy. Gene silencing of PD-L1 using small interfering RNAs (siRNAs) or micro RNAs (miRNAs) may be more efficient, however, there are barriers such as efficient

delivery, off-target effects, potential mutagenesis, and even some ethical issues that need to be addressed before this can be used clinically. Small molecule inhibitors that can either block the direct interaction between PD-1 and PD-L1 or inhibit the transcription and translation of PD-L1 or promote the degradation of PD-L1 protein, are also being investigated as alternatives or supplements to monoclonal antibodies.

Notably, antibodies to PD-1/PD-L1 demonstrate durable and persistent responses, with some patients remaining cancer free for many years. Antagonists that have been approved by FDA are all humanized monoclonal antibodies that have the ability to bind to PD-1 or PD-L1. Nivolumab and Pembrolizumab, were the first and were FDA approved in 2014. They are human IgG4 monoclonal antibody that bind to the PD-1 receptor on immune cells, most significantly cytotoxic T-cells. PD-1 and PD-L1 inhibitors are closely related to CTLA4 (cytotoxic T-lymphocyte-associated protein 4) inhibitors, such as ipilumimab.

A brief summary of the different cancer types and the antibodies used in therapy is given in Table 1.

Despite the success achieved in PD-1/PD-L1 antibody therapies, the degree of response is not as high in PD-L1 positive cohort, and some unexpected responses occurred in PD-L1 negative cohort. The cellular localization of PD-L1, intracellular versus extracellular, is believed to influence response to therapy.

Laboratory evaluation of PD-L1 [5,6]

FDA approved test/antibody clones have become available for immunohistochemistry testing. These assays have different antibodies to detect different epitopes of the PD-L1 ligand. There are different methods of scoring and thresholds set for PD-L1 positivity by IHC. The three FDA approved assays for IHC use are, PD-L1 IHC 28-8 pharmDx, PD-L1 22C3 IHC pharmDx, and Ventana SP-142.

To accurately score PD-L1 IHC stained specimens, it is critical that a minimum of 100 viable tumor cells are present for evaluation. Only the membrane staining of viable and appropriate cells that have been recommended for evaluation should be scored. Membrane staining, partial and/or complete and at all intensities (1–3+) of cells being evaluated is considered as positive staining and should be included in the scoring. Granular

Table 1. Cancer types and eligible proved PD-1/PD-L1 inhibitors.

Cancer type	PD-L1 antibody	PD-1 antibody
Non-small cell lung cancer (NSCLC)	Atezolizumab	Nivolumab, Pembrolizumab
Small cell lung cancer (SCLC)	Atezolizumab	Nivolumab
Triple-negative breast cancer (TNBC)	Atezolizumab	
Merkel cell carcinoma (MCC)	Avelumab	
Melanoma		Nivolumab, Pembrolizumab
Urothelial carcinoma	Atezolizumab, Durvalumab	Nivolumab, Pembrolizumab
Renal cell carcinoma (RCC)		Nivolumab
Hodgkin lymphoma (cHL)		Nivolumab, Pembrolizumab
Head and neck squamous cell cancer (HNSCC)		Nivolumab, Pembrolizumab
Gastric cancer		Pembrolizumab
Cervical cancer		Pembrolizumab
Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer		Nivolumab, Pembrolizumab
Cutaneous squamous cell carcinoma (CSCC)		Cemiplimab

staining must demonstrate a perceptible and convincing membrane pattern to be included. Cytoplasmic staining should not be included. (Figures 2-4).

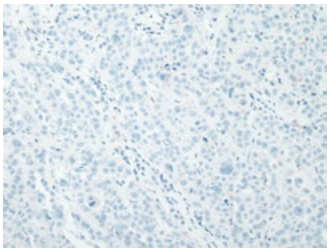


Figure 2: Tumor with negative PD-L1

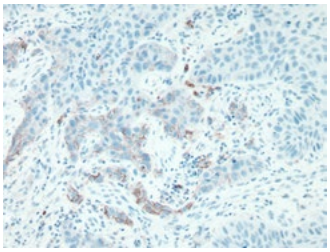
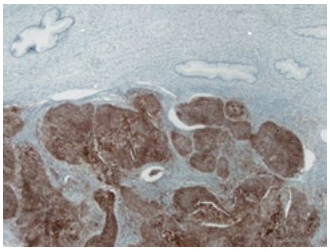


Figure 3: Tumor with positive PD-L1 (TPS of 10)



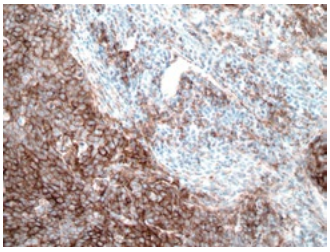


Figure 4a and 4b: Tumor with CPS of 100. Tumor cells and lymphocytes and macrophages in close contact with tumor cells are positive, while benign endocervical epithelium and inflammatory cells away from the tumor are negative.

PD-L1 expression in NSCLC is reported by using Tumor Proportion Score (TPS), which is the percentage of viable tumor cells showing positive staining. There can be heterogeneity in the staining and one should determine the overall percentage of PD-L1 positive stained tumor cells relative to the entire tumor area. The tumor is considered PD-L1 positive if the tumor proportion score is greater than or equal to 1% and TPS of 50 or more is considered as high expression of PD-L1.

$$\text{TPS} = \frac{\text{\# of PD-L1 positive tumor cells}}{\text{Total \# of PD-L1 positive and PD-L1 negative tumor cells}}$$

Other cancer types determine PD-L1 expression by using the combined positive score (CPS).

$$\text{CPS} = \frac{\text{\# PD-L1 staining cells (tumor cells, lymphocytes, macrophages) X 100}}{\text{Total \# of viable tumor cells}}$$

Although the result of the calculation can exceed 100, the maximum score is a CPS of 100.

Table 2 is a representative list of TPS/CPS cutoffs for using KEYTRUDA® (pembrolizumab) and testing using the PD-L1 IHC 22C3 pharmDx FDA approved assay.

Table 2. Companion Diagnostic Indications for Pembrolizumab

Carcinoma type	PD-L1 Expression Level
NSCLC	TPS ≥ 1%
Gastric carcinoma	CPS ≥ 1
Esophageal or Gastroesophageal carcinoma	CPS ≥ 10
Cervical Cancer	CPS ≥ 1
Urothelial Carcinoma	CPS ≥ 10
HNSCC	CPS ≥ 1

References:

1. Chen, S., Crabill, G.A., Pritchard, T.S. *et al.* Mechanisms regulating PD-L1 expression on tumor and immune cells. *J Immunotherapy Cancer* 2019; 7**:** 305

2. Tseng D, Schultz L, Pardoll D, Mackall C. 6 - Cancer Immunology. In: Niederhuber JE, Armitage JO, Kastan MB, Doroshow JH, Tepper JE, editors. Abeloff's Clinical Oncology (Sixth Edition). Philadelphia: Content Repository Only! 2020. pp. 84-96. e85.

3. Guan J, Lim KS, Mekhail T, Chang C. Programmed Death Ligand-1 (PD-L1) Expression in the Programmed Death Receptor-1 (PD-1)/PD-L1 Blockade. A Key Player Against Various Cancers. *Arch Pathol Lab Med* 2017; 141: 851-61

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5. Vaddepally, Raju K et al. "Review of Indications of FDA-Approved Immune Checkpoint Inhibitors per NCCN Guidelines with the Level of Evidence." *Cancers* vol. 12,3 738. 2020, doi:10.3390/cancers12030738

6. Udall M, Rizzo M, Faulkner E et al. PD-L1 diagnostic tests: a systematic literature review of scoring algorithms and test-validation metrics. *Diagnostic Pathology*, 2018; 13:12 doi: 10.1186/s13000-018-0689-9

UPCOMING EVENTS

GAP Virtual Presentation

Please join us on **Thursday at noon** for the following presentations:

Thursday, August 27, 12:00 noon: Melanie Bourgeau, MD and Melad Dababneh, MD, currently Pathology Residents at Emory University, will present interesting cases from Emory Pathology Services.

Do not miss this great opportunity to learn about a uterine cervix lesion, as well as microsatellite instability and DNA Mismatch Repair Systems.

Thursday, September 24, 12:00 noon: Daniel Lubin, MD will lead a thorough discussion and update us on cytopathology specimens of salivary gland lesions.

Zoom details sent via email the week of the presentations.

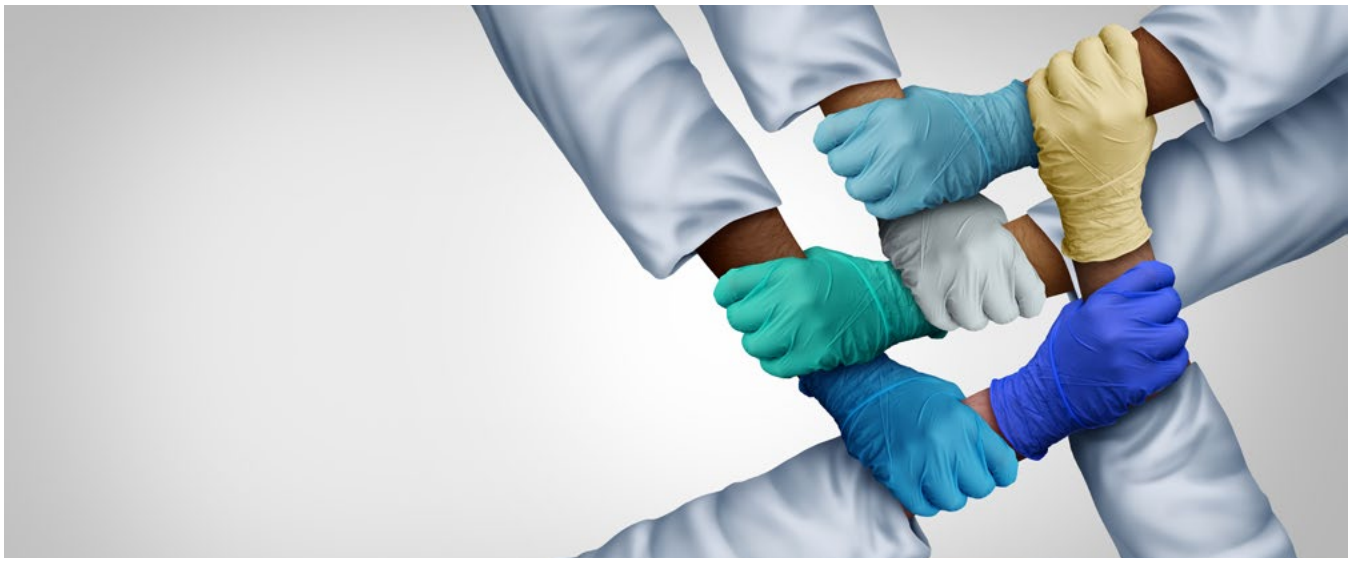
GAP Annual Meeting Going Virtual on November 7, 2020

The pandemic we are living has altered our lives and our plans.

To keep everyone safe, we are moving the annual meeting to a virtual platform on November 7, 2020.

Online registration for the virtual meeting is now open, and we encourage you to register today!

Additional information regarding the virtual meeting platform and program is coming soon.



Community Spotlight

Patrick Godbey, MD, FCAP

Joshua Alan Anderson, MD
Gastrointestinal Pathology Fellow

Uma Krishnamurti, MD PhD
Associate Professor of Pathology
Director of Surgical Pathology, Grady Healthcare System
Emory University School of Medicine
Atlanta, GA

In this issue of the GAP newsletter, we introduce a new feature that will be recurring: Community Spotlight. In each issue, we will feature a local Georgia pathologist. We hope this feature will help us get to know our colleagues in the state of Georgia and help foster a stronger sense of community.

Our first Community Spotlight is on learning more about Patrick Godbey, MD, FCAP, from his conversation with Drs. Joshua Alan Anderson and Uma Krishnamurti, from Emory University. Dr. Godbey is the CEO and laboratory director of Southeastern Pathology Associates and the laboratory director of Southeast Georgia Regional Medical Center. He is also a member of the clinical faculty of the Medical College of Georgia. He received his undergraduate degree from the University of Georgia and his medical degree from the Medical College of Georgia in Augusta. He initially practiced Obstetrics and Gynecology before completing a residency in Anatomic and Clinical Pathology at the Medical College of Georgia. He is an active member in the College of American Pathologists (CAP), holding numerous leadership positions including currently serving as president of the CAP.

What drew you to choosing Medicine as a career?

"I knew that I wanted to be a physician when I was eight years old. I was inspired by the physician who treated me when I was quite ill as a child."

What motivated you to become a pathologist?

Although Dr. Godbey knew he wanted to be a physician, his journey to the field of pathology was not direct. He initially completed a residency in OB/GYN and practiced for five years in Brunswick, Georgia.

"I had a two-month pathology elective when I was a third year OB/GYN resident. This was to help me prepare for my oral OB/GYN boards. It was during that elective that I learned what pathologists actually did and I thought it was great. The Chair of Pathology at MCG told me that if I ever wanted to change my mind, a spot in pathology would be available for me. While practicing as a gynecologist, I regularly examined specimens from my surgeries with my pathology colleagues and enjoyed that. My growing passion for pathology and the desire to spend more time with my family made me make the jump."

Dr. Godbey completed his AP/CP residency at the Medical College of Georgia. Although his journey was longer, Dr. Godbey has no regrets about switching specialties. He admits that he does miss his patients, but pathology has given him both a fulfilling career and more time to spend with his loved ones. "I made the right decision."

What do you feel is the most rewarding thing about pathology, and what do you feel is the most challenging?

"One of the most rewarding aspects of pathology is how important we are to patient care. This is exciting! Not only do pathologists play an essential role in clinical care, but also the significance of our role is constantly increasing. We have the chance to make a real difference, better our profession, and improve the care our patients receive. On the flipside, one of the most challenging aspects of our career is appropriate compensation for the increasingly essential and challenging services pathologists provide."

Dr. Godbey stressed the difficulties pathologists face on this front, including those presented by insurance companies, other third-party payers, and narrowed networks. Overall, he believes the most important legislative issue facing our specialty is the proposed 8% cut by Medicare in the next year for services given by pathologists.

What is your opinion of the GAP?

Dr. Godbey stated that the GAP is an excellent organization. He pointed out that "We need a voice" and this is through a professional state society. "Laws and regulations related to our license to practice medicine, malpractice, third party payers, etc., are largely at the state level. A state society such as the GAP is essential in getting legislative bills passed in the state that will benefit local pathologists."

He believes that state organizations such as the GAP are important both for developing a community among pathologists within their state and for advocating for our specialty at the level of state government. He wishes the GAP success in their future endeavors.

What are your hobbies and what do you do for fun in your free time?

"I enjoy many activities outside of pathology. For one, I have a great interest in renewable energy and a friend and I established the first commercial solar energy company in Georgia. I am a pilot and enjoy flying a single engine aircraft. I am also a big fan of thoroughbred horse racing."

What would be your advice to both upcoming pathologists and pathologists in practice?

To upcoming pathologists, Dr. Godbey first said, "Know that you have chosen a great career and that your future is bright." His advice is that you, "Join your state pathology society and join the CAP."

To pathologists in practice, he once again urges, "Join your state organization and the CAP and be active in these organizations." He emphasized that active engagement in legislative activity and advocacy is essential. He reiterates, when it comes to Washington and Atlanta, "If you're not at the table, you will be on the table."

COVID 19 Update:
Convalescent Serum

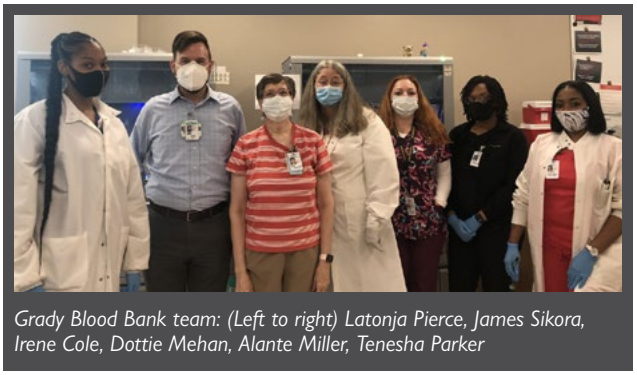
James Sikora, MD, MPH
Assistant Professor, Department of Pathology and Laboratory Medicine, Director, Transfusion Services Grady Health System, Emory University School of Medicine, Atlanta, Georgia

The practice of using plasma from individuals that have recovered from an illness is not new. Its use for the Ebola virus, influenza, and even coronavirus in recent history showed varying degrees of success. For this reason, COVID convalescent plasma (CCP) came to mind when devising strategies to fight this most recent public health pandemic. The US Food and Drug Administration (FDA) quickly approved the use of CCP for treatment of severely ill patients with COVID-19.

Potential donors of CCP are contacted by the blood suppliers (or the patients are referred by clinical teams) to explore whether or not they qualify as a CCP donor. If the donor qualifies, the CCP product is tested to ensure safety for transfusion as well as the level of antibodies present in the plasma to COVID-19. The plasma is frozen until requested for a specific patient. Once requested for a patient, it is thawed at the blood bank where the product will be transfused.

Nation-wide studies are ongoing to provide CCP to patients in need while adhering to strict protocols to allow for reliable data collection. The Mayo Clinic spearheads one of the largest studies known as the COVID-19 Expanded Access Program. To enroll, visit the website uscovidplasma.org to join and learn about CCP. The Biomedical Advanced Research and Development Authority (BARDA) covers the cost of the CCP in this study. There are currently over 2,500 sites participating in this study with over 41,000 patients.

The benefit of transfusing CCP is the possibility of decreasing the severity of a COVID-19 infection. The CCP supply is growing with the number of infections, which allows for a generous stockpile. CCP is also less expensive than other treatments that are available currently. However, as we understand more about COVID19 and the disease associated



Grady Blood Bank team: (Left to right) Latonja Pierce, James Sikora, Irene Cole, Dottie Mehan, Alante Miller, Tenesha Parker

with it, there is reason to believe that possible harm could also come from the administration of CCP. We now know that COVID-19 alters the coagulation process, and the safety of transfusing a product that increases coagulation may not be as safe as initially thought. Transfusion transmitted diseases, although a small risk with current testing and methods, is still of concern with giving any blood product. Transfusion reactions may also occur with the administration of CCP and should be investigated in the usual fashion as with any blood product.

Although approved by the FDA, CCP is an experimental treatment. It has not been widely studied for use in COVID-19 and needs review in thorough protocols before considering it a proven treatment. There is hope that this is one of the tools that healthcare will have against this pandemic and others that may follow. It is important to monitor the upcoming findings associated with CCP so that we will be able to guide clinicians on the proper use.

If interested in learning more about this subject there are recent publications available (excellent review by Sullivan and Roback in Transfusion Medicine Reviews) and the blood supplier websites (American Red Cross, LifeSouth, OneBlood, etc.) have useful information.

CASE PRESENTATION

Correct answer:

*The correct answer is **B**.*

Explanation of the correct answer:

The lesion is granular cell tumor (GCT) with overlying Pseudoepitheliomatous hyperplasia (PEH) mimicking an invasive squamous cell carcinoma.

Sections show a tongue biopsy with florid squamous epithelial hyperplasia overlying a tumor composed of S-100 positive plump polygonal cells with small nuclei and abundant eosinophilic granular cytoplasm. The cytoplasmic granules are composed of phagolysosomes that are PAS positive and diastase resistant. The tumor cells are also positive for SOX10 and CD68.

Option A: Peripheral nerve tumors such as schwannomas and neurofibromas, also S100 positive, may show some granular changes but rarely create a major diagnostic challenge with GCT. In addition, schwannomas are encapsulated, and other stigmata of von Recklinghausen disease seen with neurofibromas are not found in patients with GCTs.

Option C and D: PEH can rarely be found in association with basal cell carcinoma (BCC) but the epidermal hyperplasia has a follicular differentiation and is often eccentric relative to the BCC rather than directly overlying it. Leukoplakia and erythroplakia are precursor lesions for oral squamous cell carcinoma (SCC). Differentiating PEH from invasive SCC especially on superficial and limited biopsies can be extremely challenging.

PEH Clinical findings and/or the presence of an underlying reason for the presence of PEH can tilt the diagnosis in favor of PEH, although few cases of coexistence of PEH and SCC have been reported. SCC is favored by more pronounced cytologic atypia and other features of overt malignancy such as increased mitotic activity (especially presence of atypical mitoses) and perineural/lymphovascular invasion which are not seen in this case.

A brief summary of the pathologic features of this entity

Granular cell tumor (GCT), also named Abrikossoff's tumor, granular cell myoblastoma, granular cell nerve sheath tumor, and granular cell schwannoma, is a relatively uncommon neoplasia, that typically arises in the third to the sixth decades, with slight female preponderance.

Anatomical distribution includes cutaneous, subcutaneous, or visceral sites and the most frequent localization is the head and neck region, with the highest prevalence in the tongue. Histologically, GCT is characterized by plump polygonal cells with small nuclei and abundant eosinophilic granular cytoplasm. Pseudoepitheliomatous hyperplasia (PEH) do occur in lesions of granular cell tumor – typically in the overlying epithelium – and often mimic invasive squamous cell carcinoma (SCC), although there have been reports of the coexistence of PEH and invasive SCC. The exact explanation for the association between GCT and PEH is unknown but is postulated to be due to the proliferative activity of basal cells that interact with granular cells and neighboring epithelial cells.

PEH (also known as pseudocarcinomatous hyperplasia, invasive acanthosis, verrucoid epidermal hyperplasia and carcinomatoid hyperplasia) is a reactive epithelial proliferation found in association with several neoplastic and reactive processes. Histologically, it is seen as cords and strands of squamous epithelium that extends to the underlying dermis or submucosa displaying a pseudo-infiltrative pattern of growth and closely mimicking invasive squamous cell carcinoma. However, classic cytologic sign of malignancy are not seen. In contrast, SCC characteristically shows cytological atypia such as nuclear pleomorphism, increased mitotic activity and infiltrative growth pattern.

A properly oriented H and E–stained section is the gold standard for diagnostic interpretation, however most biopsy are small and suboptimal posing diagnostic challenges. Some authors suggest that in occasional doubtful cases PEH may be distinguished from SCC by the combined use of p63 and Ki-67 (p63 and Ki-67 are more prominent and localized in SCC compared to PEH). Another study by Zarovnaya and Balck showed that p53, matrix metalloproteinase 1 (MMP1) and E-cadherin can be utilized to distinguish PEH from SCC (SCC more likely than PEH to showed increased staining for p53 and MMP-1 and decreased staining for E-cadherin).

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