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Louisiana Physicians Are Increasing HPV Vaccination Rates

Donna Lisa Williams, DrPH, Courtney Suzanne Wheeler, MPH, Michelle Lawrence, MPH
Stacy Stevens Hall, RN MSN, Michael Hagensee, MD

Human papilloma virus (HPV) is a common virus that can cause genital warts and certain cancers. The HPV vaccine is effective in preventing many HPV-associated diseases, however, vaccination rates suggest many remain unprotected. This study examined successful strategies used by physicians to improve HPV vaccination rates.

Providers with above average vaccination rates were identified. A representative from each provider participated in an interview to identify strategies used to boost HPV vaccination.

Key strategies in ensuring vaccine completion were reminders, education, standing orders, and scheduling future vaccine appointments at time of first dose. Other successful strategies included coupling the HPV vaccine with adolescent vaccines, administering during well-visits, and recommending the vaccine as protection against cancer and genital warts.

Findings suggest successful and widely used methods among high performing providers in Louisiana, the majority of which should be easily reproducible with minimal resources to improve HPV vaccination rates.

INTRODUCTION

Human papillomavirus (HPV) is a common virus that has been shown to cause genital warts, as well as anogenital and oropharyngeal cancers. In fact, HPV is estimated to cause close to 27,000 cancers each year in the U.S. and an average of 1,429 cancers annually in Louisiana. Most cervical cancers are caused by HPV, but so are a majority of the cancers of the vagina, vulva, penis, anus, and throat.

The first HPV vaccine was approved by the Food and Drug Administration over a decade ago, and the various iterations of the vaccine have been shown to be effective in preventing cervical cancer and other HPV-associated cancers and genital warts. Vaccines are available for males and females ages 9–26, however, the federal Advisory Committee on Immunization Practices (ACIP) has recommended routine vaccination for male and female adolescents ages 11–12.

Under the Affordable Care Act, most health plans must cover a defined set of preventive services with no cost-sharing by the patient, including HPV vaccination for children from age 11-21. The included health plans are Medicaid, the plans in the insurance marketplace, most small and large group plans, and most employer self-insured plans. While some plans existing before 2010 were grandfathered in and not required to provide the preventive services with no cost-sharing, the percentage of plans falling into this category is decreasing, and, over time, most plans will lose this status.

Despite evidence that the vaccine is effective in reducing infection and its coverage by most insurances, rates remain below the Health People 2020 recommendation of 80%, suggesting that many in the U.S. remain unprotected. The 2015 National Immunization Survey (NIS) results for completing all three shots in the HPV series for females was 39.3% and for males was 30.5% in Louisiana, both of which are significantly lower than the Healthy People 2020 target of 80% vaccination coverage. In October 2016, the Centers for Disease Control and Prevention changed its recommendations to a two shot series for adolescents under 15. While this should ease some of the barriers associated with series completion, with only 60.3% of females and 49.5% of males initiating the series in Louisiana in 2015, there is still a great deal of room for improvement.

Previous research examined various methods used to increase vaccine uptake. These strategies range from educating both the providers and parents/adolescents to system changes, such as implementing standing orders or a reminder recall system. The study by Cassidy et al. supports the benefit of provider recommendation; 78.3% of parents mentioned that a recommendation from the providers aided in their decision to vaccinate. This study, as well as others, illustrate the benefit of patient reminders. Other studies have found that shot records helped to improve vaccination rates.

In examining vaccination providers in Louisiana, it was obvious that some providers were having better HPV vaccination outcomes compared to other providers in the state (unpublished data). So what strategies are pediatricians and other healthcare providers in Louisiana using to increase the HPV vaccination rate and how can these strategies be used in any practice? The intent of this study was to discover uncommon but successful strategies providers can implement in their practices at little to no cost to increase initiation and completion of the vaccine series.
METHODS

This study sought to identify uncommon but successful behaviors that lead to better outcomes in HPV vaccination. The purpose was to identify best practices used by top performers. This qualitative study was conducted by the Louisiana Cancer Prevention and Control Program (LCP) with assistance from the Louisiana Department of Health Office of Public Health Immunization Office. The Immunization Office identified providers with above average HPV vaccination rates based on total volume of vaccine administered compared to all providers in Louisiana. The volume of vaccine administered was determined by utilization of the Immunization information system, Louisiana Immunization Network for Kids Statewide (LINKS), for inventory management. Three high-volume providers were identified in each of the nine public health regions in the state. Additional inclusion criteria were: 1) the key informant had to be 18 years or older, 2) be a healthcare provider or clinic director/administrator, and 3) providers must participate in Louisiana’s childhood immunization program and be English speaking. As a result, 28 providers were identified as having above average vaccine uptake. Of the 28 providers, 25 were pediatric clinics. The three remaining clinics offered services across age ranges. This study was approved by the Institutional Review Board.

The selected providers were contacted via letter from the Louisiana Immunization Office to explain the study and were asked if they agreed to be contacted by LCP. Contact information was then given to LCP to conduct key informant interviews.

Structured interviews were conducted with a representative from each of the twelve providers who participated in the study. The interviews were conducted using an interview guide developed by LCP to explore strategies providers used to increase HPV vaccine uptake. The interview guide included questions to elicit information on provider demographics and strategies used to increase HPV vaccination. General topics assessed were provider policies and procedures, provider-parent interaction, and provider strategies to increase HPV vaccination. Interviews were conducted over the phone and recorded with participant permission.

Statistical Analysis

Interviews were recorded for transcription and analyzed using NVivo11 qualitative analysis software. Interviews were linked with providers’ demographic data in NVivo. Each interview was independently coded. This was an iterative process. After completion of the independent coding, the authors came together to review the codes and identify common themes (Table 1). Differences were resolved through consensus.

RESULTS

Twelve of the 28 providers agreed to participate in the study. The 16 providers that did not participate either did not return calls to schedule an interview, chose not to participate, or a representative was not able to answer interview questions. The participants came from seven of the nine public health regions of the state and seven of the 64 parishes in the state. The sample consisted of providers whose patient populations were entirely or partially children, ages 0–18. Six providers had a patient population of 100% children. The remaining providers had patient populations of at least 85% children. The majority (79%) of the patient populations of the participating providers had family incomes below 200% of the federal poverty level.

Themes identified through the analysis are shown in Table 1. The interviews showed that high-performing providers used a variety of strategies to get parents and youth/adolescents to initiate and complete the three-dose HPV vaccine series: education, standing orders, reminders, and scheduling vaccine appointments during current appointment. Other successful strategies included coupling the HPV vaccine with adolescent vaccines, administering during well visits, recommending the vaccine, and indicating that the HPV vaccine protects against cancer (Figure 1).

These researchers discovered that examining shot records helped providers stay abreast of patients that were eligible for the vaccine. As a result, patients and parents were able to receive education about the vaccine or the vaccine itself at well child visits or other doctor appointments.

The most frequently used strategies (Figure 1) were education (n=11) and standing orders (n=11), followed by reminders (n=10) and scheduling appointments for doses two and three during the current visit (n=8). Other strategies that were used moderately often include: offering the HPV vaccine with the other adolescent vaccines (n=6), indicating that the vaccine can protect against cancer (n=6), recommending the vaccine to patients (n=6), and offering the vaccine during well visits (n=6). The least frequent strategy reported by providers was informing parents that their insurance may cover the cost of the vaccine, thereby removing cost as a barrier (n=1) and only two providers indicated discussing the association of HPV infection with sexual activity.

Specific provider comments regarding strategies to increase HPV vaccination rates are detailed in Table 2.

Figure 1. Strategies used by providers to increase vaccination rates
Themes | Child Codes
--- | ---
Appointment | Patient given appointment for vaccination during current visit
Education | • Cards • Informational Posters • Talking
• Drug Rep • Nursing Staff • Tape (video)
• Handouts • Pictures
Insurance | Insurance is seen as a barrier or facilitator to receiving vaccines
Adolescent Vaccines | HPV vaccine is offered as an adolescent vaccine or along with other adolescent vaccines (Meningitis or Tdap)
• 11 yr. old • 12 yr. old • Meningitis
Prevent Cancer | Reason for getting HPV vaccine is cancer prevention
Protect | HPV vaccine is seen as protection against cancer or genital warts
Recommendation | • Offer vaccine during current office visit • Recommend vaccine during current office visit
Relationship | Building a relationship with patient aids in HPV vaccination
Reminders | • Calls • Postcard • Text Message
Sexual Activity | HPV vaccine is associated with sexual activity
Shot Records | Clinic checks shot records to determine what vaccines patient is eligible for during visit
Standing Orders | Clinic has standing orders for vaccines, may or may not include HPV
Well Visit | HPV vaccine is talked about, offered or given during well visit

**DISCUSSION**

Studies have shown that a physician recommendation may be the most important factor in HPV vaccination adherence, and according to Reiter, et al., vaccine initiation is higher among parents who receive such recommendations. At least one study has found that pediatricians and family physicians are reluctant to recommend the vaccine because of the perceived necessity to discuss sexual activity in children. However, one systematic review found that only 6-12% of parents indicated a concern that the vaccine would promote sexual activity across the studies reviewed. Another study, a systematic review of European studies, found that parents of children who had received prior vaccines had higher rates of acceptance of the HPV vaccine in all 23 studies reviewed. Along with these studies, our findings support the idea that physicians may be more successful by including the vaccine in their general recommendations for vaccines and limiting such discussion only to those families who ask. In fact, the CDC suggests recommending the HPV vaccine in the same way that other child and adolescent vaccines are offered, that is without lengthy discussions on transmission.

Many physicians miss the opportunity to recommend and administer the vaccine at crucial 11 or 12-year wellness visits. This study discovered several approaches to reducing these missed opportunities. This includes having standing orders for HPV vaccination and making that recommendation at every visit, well or sick. Other successful providers simply included the vaccine in the list of recommendations for the 11 or 12-year well visit. Combining both approaches should significantly decrease

missed opportunities.

The findings of this study included the use of reminder calls and text messages and scheduling appointments for subsequent doses at the time of the first dose to increase adherence to series completion. While moving to a two-dose series should facilitate completion, further investigation is warranted on systems changes including alternative hours and sites for vaccination to overcome the barriers to completing the series.

While insurance coverage was not mentioned frequently by those interviewed, informing parents about their coverage could reduce hesitancy related to financial burdens. According to the 2015 Louisiana Health Insurance Survey, 59.6% of children in Louisiana are covered by Medicaid, which covers vaccination at no cost to parents. Of children in Louisiana, in 2016 less than 4% had no health insurance and less than 7.5% and dropping were covered by grandfathered plans and could be expected to have out of pocket expenses for vaccination. This leave approximately 90% of children in Louisiana fully covered for HPV vaccination.

There are some limitations to this study. The sample size is small and involves clinics with a large population of patients under 200% FPL and covered by Medicaid. Therefore, the same strategies may not be applicable to providers with patients who are above the federal poverty level, are largely covered by private insurance, have significantly smaller or larger patient populations or are located in rural or suburban area.

The practices are summarized in Figure 2. The next steps in this process will be to design ways to allow other providers to practice these behaviors and monitor the effectiveness of such practices. To that end, the Louisiana Immunization Work Group has been formed with the mission of improving immunization rates through coordinated activities and sharing of information. The partnership includes the Louisiana Department of Health Immunization Program, medical society chapters including the Louisiana Chapter of the American Academy of Pediatrics, cancer programs such as the American Cancer Society and the Louisiana Cancer Prevention and Control Programs, immunization partners, health systems, and insurance partners.

**CONCLUSION**

This study uncovered successful and widely used methods among high performing providers in Louisiana. The majority of these strategies require simple system changes within the practice that should be easily reproducible to improve HPV vaccination rates. Further, these practices require minimal resources and most if not all can easily be implemented in any practice. Collaborative efforts are underway in Louisiana to disseminate these and other practices.
What Louisiana Healthcare Providers Are Saying

<table>
<thead>
<tr>
<th>Theme</th>
<th>Quote</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education</td>
<td>“We start educating parents then on what HPV is. I always give them the statistics on the amount of our the population estimated to already have HPV and not even be aware of it because it is typically asymptomatic so the parents are just very receptive...” (Interview 7)</td>
</tr>
<tr>
<td>Standing Orders</td>
<td>“We do have standing orders and yes it includes HPV vaccinations and all the vaccinations that we give.” (Interview 1)</td>
</tr>
<tr>
<td>Reminders</td>
<td>“...we have a pamphlet about how they can sign up for text messaging... we give a reminder call about all of our appointments the day before so we try to remind them to come in and then we send out patient reminders to go through the LINKS system.” (Interview 12)</td>
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<tr>
<td></td>
<td>“...we have what is called Televox and what it does is call the home and gives them friendly reminders of their appointment and we usually do it two or three days ahead of the appointment time... Then we have Televox give them an appointment for the next time and we have Televox to remind them of the appointment. So the Televox will call them and let them know that they have an appointment on whatever day it is and there it is located.” (Interview 6)</td>
</tr>
<tr>
<td>Appointments</td>
<td>“We would also schedule the next visit at the current visit and that really helps with completion...” (Interview 3)</td>
</tr>
<tr>
<td>Protects Against Cancer</td>
<td>“I let them know that it protects them against the cervical, oral, and anal cancers and that it takes all three (shots)...” (Interview 1)</td>
</tr>
<tr>
<td>Group with Other Vaccines</td>
<td>“...we just grouped into the 11 year old vaccine with tetanus and meningitis vaccine.” (Interview 3)</td>
</tr>
<tr>
<td>Include in Well Visit as Well as Any Other Visit</td>
<td>“We try to make sure that they are up to date on their wellness visits and when they do come in for their wellness visits their shot records are reviewed as well as when they come in for other office visits.” (Interview 10)</td>
</tr>
<tr>
<td>Make the Recommendation</td>
<td>“We start offering it when they come in for their 11 year old visits and most of them pretty much say that they will get it but each visit they come in and we see that they don't have the Gardasil, then we offer it to them again and ask them if they have any questions and have the doctors back us up to try to get them vaccinated...” (Interview 12)</td>
</tr>
<tr>
<td>Make the Recommendation</td>
<td>“We go over their shot records pretty much every visit. Whether they come in sick or well or whatever, we try to keep up with them. We have thousands of kids linked here so it's very difficult. We try to make sure that they are up to date on their wellness visits and when they do come in for their wellness visits, their shot records are reviewed as well as when they come in for other office visits. If we see that they are past due for shots, even if they are sick and can't give them, we tell them to schedule an appointment in 7-10 days for a recheck and possibly to get their shots.” (Interview 10)</td>
</tr>
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Table 2. What Louisiana Healthcare Providers are Saying

7 Ways to Improve HPV Vaccination Rates

1. PROVIDER RECOMMENDATION - Advocate for your patients to receive the HPV vaccine. Your recommendation is a large motivating factor.

2. COMBINE WITH OTHER VACCINATION SCHEDULES - Group the HPV vaccination in with the 11 or 12 year old vaccines.

3. SCHEDULE THE NEXT APPOINTMENT DURING THE CURRENT VISIT - Automatically set up the next vaccination visit during the current visit to ensure patients complete the series.

4. PROVIDE REMINDERS - Provide patients with a reminder card when the appointment is made. Follow up with a phone call, postcard, or text message.

5. USE STANDING ORDERS - Make the HPV vaccination a standing order in your clinic for those ages that are eligible to get the vaccine.

6. RECOMMEND AT EVERY CHECK UP - Recommend the HPV vaccination at every well visit or check-up. This provides more than one opportunity to vaccinate and reminds patients that it is important.

7. INSURANCE COVERS IT - Remind your patients that the vaccine is covered by insurance.

Figure 2. Seven Way to Improve HPV Vaccination Rates

ACKNOWLEDGEMENTS

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Donna L. Williams, DrPH, is associated with the Louisiana State University Health Sciences Center, School of Public Health; Courtney S. Wheeler, MPH, is associated with the Centers for Disease Control and Prevention; Michelle Lawrence, MPH, is associated with the Louisiana State University Health Sciences Center, School of Public Health; Stacy S. Hall, RN MSN, is associated with the Louisiana Department of Health, Office of Public Health Immunization Program; Michael Hagensee, MD, PhD, is associated with the Louisiana State University Health Sciences Center, School of Medicine.
Acute Promyelocytic Leukemia and Chronic Lymphocytic Leukemia: Concomitant Presentation of Two Molecularly Distinct Entities

Jingdong Su, MD, Diana Veillon, MD, Rodney Shackelford, MD, James Cotelingam, MD, Hazem El-Osta, MD, Glenn Mills, MD, Reinhold Munker, MD, and Srinivas Devarakonda, MD

Acute myeloid leukemia (AML) developing in patients with chronic lymphocytic leukemia (CLL) is very uncommon and usually associated with prior treatment. Acute promyelocytic leukemia (APL) accounts for a very small proportion of treatment-associated AML. So far, there has been only one reported case of APL occurring post radiation for prostate cancer in a patient with CLL. We report herein the first case of APL and CLL presenting concomitantly in an untreated patient. Evaluation of peripheral blood and bone marrow aspirate with immunohistochemistry, flow cytometry, and FISH to confirm two morphologically, molecularly and genetically distinct leukemic populations characteristic of APL and CLL is required. APL is a hematologic emergency, and aggressive management is vital to a successful therapeutic outcome. Standard treatment is with All-trans retinoic acid (ATRA) and anthracycline-based regimen, whether the process is de novo or therapy-related. Due to increased incidence of secondary malignancies in CLL patients, active surveillance is necessary.

INTRODUCTION

Secondary malignancies following treatment of chronic lymphocytic leukemia (CLL) and other malignancies are common. These include solid tumors as well as hematologic malignancies.1,2 Acute myeloid leukemia (AML) occurring after treatment for other malignancies is frequently reported. However, AML following treatment of CLL patients is extremely rare. Although acute promyelocytic leukemia (APL) accounts for 12-15% of therapy-associated AML, these cases typically occur following chemotherapy with topoisomerase II inhibitor and only occasionally following radiation therapy.3-6 To our knowledge, concomitant APL and CLL in untreated patient have not been found in literature, prompting this report.

CASE REPORT

A 52-year-old Caucasian male with a past medical history of hypertension, insulin-dependent diabetes mellitus, and coronary artery disease status post stent placement presented initially to an outside facility with substernal chest pain and dyspnea for two days. He did not report any fatigue, drenching night sweats or weight loss. On examination, there was no evidence of lymphadenopathy, splenomegaly or hepatomegaly. No petechiae or ecchymosis were evident. Complete blood count showed a white blood cell count (WBC) of 17,000 /µL comprised of 97% lymphocytes and 2% blasts, hemoglobin of 6.0 g/dL, and a platelet count of 16,000 /µL. He was found to have an elevated serum troponin 0.30 ng/mL (normal range 0 - 0.05 ng/mL). Other laboratory studies were unremarkable. Electrocardiogram (ECG) revealed ST-depression in lateral leads suspicious for a non-ST elevation myocardial infarction (NSTEMI). On admission, he received packed red blood cell and platelet transfusions with resolution of chest pain.

NSTEMI was conservatively managed due to thrombocytopenia. Work up for infection was negative. WBC count further increased to 69,000 /µL and platelet count decreased to 9,000 /µL. Coagulation studies revealed a slightly elevated prothrombin time (PT) of 16.7 seconds, normal activated partial thromboplastin time (aPTT), and normal fibrinogen.

Peripheral blood smear examination revealed conspicuous atypical lymphocytes and occasional promyelocytes. On immunohistochemical staining (BenchMark ULTRA automated stainer, antibodies from Ventana Medical Systems, Inc., Tucson, AZ), these cells were positive for myeloperoxidase (Figure 1G) and CD117, but negative for CD34. The remaining 35% of the marrow cellularity was comprised of small atypical B lymphocytes. These cells expressed CD20 (Figure 1H) and BOB-1 on immunohistochemical staining, but did not express CD20. Other hematopoietic elements were virtually absent. Flow cytometric studies performed on the bone marrow aspirate revealed a prominent population of leukemic promyelocytes with expression of CD13, CD15, CD33, CD56, and CD117. CD45 expression was dim. CD34 and HLA-DR were negative. A population of clonal B cells was identified that expressed CD5, CD19, CD20 (dim), CD22, CD23, CD45, and HLA-DR, and were kappa light chain restricted. Molecular genetic studies by fluorescence in situ hybridization (FISH) were positive for PML/RARA with PML/RARA fusion signals identified in 122/200 cells (Figure 1D). Molecular genetic studies by FISH for CLL associated prognostic abnormalities detected a deletion in 13q. Morphologic features, flow cytometric findings, and molecular genetic studies were diagnostic of an acute promyelocytic leukemia (APL) with t(15;17)(q22;q21); PML/RARA and concomitant B cell chronic lymphocytic leukemia (CLL).
considered in the differential diagnoses. Broad spectrum antibiotics were continued and diuretics as well as non-invasive ventilation with bi-level positive airway pressure (BiPAP) were applied. Despite aggressive medical management, patient’s condition deteriorated rapidly and he died from multi-organ failure within forty-eight hours of his presentation.

**DISCUSSION**

Chronic lymphocytic leukemia (CLL) is the most common form of adult leukemia in the western hemisphere. The treatment of CLL is associated with a high incidence of secondary malignancies including non-melanoma skin cancer, Kaposi sarcoma, melanoma, cancers of the lung, gastrointestinal tract, breast, prostate, kidney, bladder, head and neck, and transformation to an aggressive large B-cell lymphoma (Richter’s syndrome). It is noteworthy that AML developing in a background of CLL is extremely rare. Among those with treatment-associated AML (t-AML), exposure to topoisomerase II inhibitors (mainly Etoposide), alkylating agents and ionizing radiation are among the main contributing factors. Cases of AML have also been reported in patients treated with other topoisomerase II inhibitors such as Mitoxantrone and Bimolane. AML after treatment with DNA-topoisomerase II inhibitors has a short latency period, presents without a prior myelodysplastic syndrome, and is associated with 11q23 translocation.

In 2006, there were two reports of concurrent AML with CLL in untreated patients. Gottardi et al documented simultaneous CLL and AML (FAB-M2) based on morphological and immunologic features. The AML component was CD34+/CD13+/HLA-DR+/CD7+, and the CLL expressed VH3-53/D3-22/JH4 Ig with 3.9% IgVH mutations. Further evaluation with IgH gene rearrangement on CD34+/CD19- and CD34-/CD19+ immunomagnetically sorted cell populations revealed a shared molecular signature suggesting that genomic DNA from the CD34-/CD19+ cell fraction demonstrated IgH gene rearrangement, resulting in expansion of two independent clones and concomitant presentation of CLL and AML. In the case reported by Lu et al, cytogenetic analysis revealed inv(16)(p13.1q22) and trisomy 22 in a second clone. Fluorescence in situ hybridization confirmed the CBFβ rearrangement associated with inv(16) in myeloblasts and myelomonocytic cells but not in CLL cells, confirming that the AML and CLL did not share clonality.

The association between APL and CLL is even rarer. Molero et al reported a case of APL that developed two years after radiotherapy for prostate cancer in a patient with chronic lymphocytic leukemia. Although no treatment was given for the patient’s CLL, radiotherapy for prostate cancer in this patient might have contributed to the development of APL and is considered therapy-related. It has been suggested that there is a 0.1 – 0.2% risk of developing AML within 10 years in patients receiving radiation therapy, and the incidence is higher in patients with a mean bone marrow dose of greater than 3.5 Gy. To date, no report in the literature has been found on simultaneous occurrence of APL and CLL in patients without

**Figure 1.** Peripheral smears, bone marrow aspirate, H&E and IHC staining show two distinct populations of leukemic cells. 1A. Peripheral blood smear showing CLL lymphocytes (Wright-Giemsa X 1000). 1B. Peripheral blood smear showing a leukemic promyelocyte, CLL lymphocyte, and a smudge cell (Wright-Giemsa, X 1000). 1C. Bone marrow aspirate showing several leukemic promyelocytes and a single CLL cell (Wright-Giemsa stain, X1000). 1D. Bone marrow aspirate. Positive FISH result with PML/RARA fusion identified in leukemic promyelocytes (15q22-24 LSI PML Spectrum Orange/17q21 LSI RARA Spectrum Green, X1000). 1E. Bone marrow clot section with a central focus of CLL surrounded by leukemic promyelocytes (Hematoxylin & Eosin, X 100). 1F. Bone marrow clot section showing the interface between CLL and APL (Hematoxylin and Eosin, X 400). 1G-H. Bone marrow clot section showing the interface between APL cells stained positive for myeloperoxidase (G) and CLL cells stained positive for CD79a (H) (Immunohistochemical staining for Myeloperoxidase and CD79a, X 400).
any previous treatment, either for CLL or for other co-existing conditions. In our patient, further evaluation of CLL by FISH studies detected a deletion of 13q14.3. Common cytogenetic abnormalities associated with CLL include trisomy 12, del(13)(q14.3), del(11)(q22.3), and del(17)(p13.1). Isolated deletion of 13q14.3 as seen in our patient is considered a favorable prognostic marker in the absence of other adverse genetic markers. Based on the morphology, immunohistochemistry, cytogenetic and molecular analysis, it is apparent that our patient had co-existence of two unrelated hematological malignancies.

APL is a hematological emergency that is managed the same whether the disease is de novo or therapy-related. Treatment with ATRA should be initiated immediately. Anthracycline-based treatment and arsenic trioxide (ATO) as part of induction chemotherapy is recommended in patients with adequate cardiac function. Since disseminated intravascular coagulation (DIC) occurs in up to 85% of patients, coagulation studies should be monitored frequently, and DIC should be corrected aggressively by transfusion with fresh frozen plasma (FFP) and cryoprecipitate.

**CONCLUSION**

We report herein an extremely rare case of concurrent APL and CLL. To the best of our knowledge, this is the first report of APL presenting simultaneously with CLL in a patient without prior treatment. In addition to the distinct morphology of the leukemic components, the diagnosis was confirmed by molecular genetic and flow cytometric studies. Aggressive treatment should be initiated as soon as APL is suspected to avoid serious complications.

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Jingdong Su, MD, is associated with the Department of Hematology/Oncology, LSU Health Sciences Center-Shreveport; Diana Veillon, MD, is associated with the Department of Pathology, LSU Health Sciences Center-Shreveport; Rodney Shackelford, MD, is associated with the Department of Hematology/Oncology, LSU Health Sciences Center-Shreveport; James Cotelingam, MD, is associated with the Department of Pathology, LSU Health Sciences Center-Shreveport; Hazem El-Osta, MD, is associated with the Department of Hematology/Oncology, LSU Health Sciences Center-Shreveport; Glenn Mills, MD, is associated with the Department of Hematology/Oncology, LSU Health Sciences Center-Shreveport; Srinivas Devarakonda, MD, is associated with the Department of Hematology/Oncology, LSU Health Sciences Center-Shreveport.
Transvenous Before Surgical Hybrid Procedure
Joseph J. Tiano, MD, Robert Drennan, MD, John Novella, MD, Rafael Squiteri, MD, Malcolm Robinson, MD, Albert DiMeo, MD, Lindsey Scierka, MPH, Paul LeLorier, MD

Background: Historically, persistent atrial fibrillation (PeAF) and long standing persistent atrial fibrillation (LSPeAF) have demonstrated limited clinical success despite hybrid approaches.

Objective: We describe our experience with the endocardial-before-epicardial approach defined by a comprehensive endovascular approach preceding and guiding the epicardial approach which includes an extensive posterior wall ablation.

Methods: 40 patients were followed over a 12 month period. The procedure was performed in a single center. Patients had a mean duration of atrial fibrillation of 6.0 ± 4.5 years with 22.5% having undergone prior ablations. Mean age was 61.7 ± 7.9 years with a mean left atrial volume of 131.5 ± 46.9 mL. The endovascular procedure remained uniform with antral pulmonary vein isolation, posterior left atrial roof and right atrial cavo-tricuspid isthmus (CTI) linear lesions with mapping and ablation of left atrial complex electrograms (CFAEs) and prior existing atrial arrhythmias. The epicardial procedure included a thorascopic approach with ganglionated plexus (GP) mapping and ablation, left atrial posterior wall ablation, directed CFAE ablation and left atrial appendage ligation. All patients received implantable cardiac monitoring.

Results: All 40 patients remained in sinus rhythm at their 12 month follow-up. During the monitoring period, episodes of paroxysmal atrial arrhythmias including fibrillation were documented, without persistence, after discontinuation of oral antiarrhythmic medications.

Conclusion: The endo-before-epi approach resulted in improved management of persistent and long standing persistent atrial fibrillation over reported results for conventional approaches with no procedural complications, making this a promising option for the management of these arrhythmias.

INTRODUCTION
Atrial fibrillation (AF) is the most common chronic arrhythmia requiring treatment in Western society and has become a major health burden. The risk of developing AF from age 40-95 is 26% in men and 23% in women. In the ATRIA study it was estimated that 2.3 million adults in the U.S. had AF in 2006 and 2007 and that this will increase to 5.6-7.6 million by the year 2050. Unfortunately, medical management with either rate or rhythm control has yielded suboptimal clinical results leading to further development and advancement of non-pharmacological strategies, including both surgical and endovascular ablations. For patients with documented paroxysmal AF (PAF), catheter-based pulmonary vein isolation has resulted in acceptable results, but long-term success remains disappointing for patients with persistent and long-standing persistent atrial fibrillation. This has led to further refinements in non-pulmonary vein targets including ganglionated plexi, ectopic foci, rotors, and macro re-entrant circuits that enable arrhythmogenic wave fronts. Unfortunately, the addition of lesion sets to address extra-pulmonic substrate does not always lead to higher success rates. Thus, the five year arrhythmia-free survival in non-paroxysmal atrial fibrillation (NPAP) for a single endocardial catheter ablation procedure still remains low and has been reported at 28.4% with the efficacy after multiple procedures at 51.1%. Surgical AF ablation also has evolved from the original open Cox Maze procedure, which never gained widespread acceptance due to its technical complexity and invasiveness, to a much more minimally invasive, video-assisted thoracoscopic approach with bipolar radiofrequency ablation (other energy modalities having come and gone) via clamping and pen with adequate results.

However, there still remains difficulty in achieving durable transmural lesions by means of a thoracoscopic approach alone and recurrent atrial arrhythmias can often be seen, up to a 40% rate with one year follow up in an early paper on the subject. Furthermore, confirmation of block and mapping of arrhythmias via an epicardial approach when working alone remains limited and difficult, possibly leading to suboptimal results. This has led to the development of the hybrid AF ablation techniques utilizing both a surgical epicardial approach along with a transvenous endocardial approach, attempting to harness the benefits of each strategy while mitigating their shortcomings and hoping to achieve a synergistic benefit. Currently the two most commonly used minimally invasive approaches in performing the epicardial ablation is either a thoracoscopic approach or a pericardioscopic approach. Commonly, the surgical portion of the hybrid approach is prior to the transvenous portion in a staged approach, thereby, in principle, allowing the electrophysiologist to confirm epicardial linear lesions and pulmonary vein isolation (PVI); in addition to decreasing the burden of additional endocardial lesion sets needed to be applied by the electrophysiologist to achieve procedural end-points. While hybrid approaches have
yielded improved outcomes at one year over either approach alone, success rates, particularly beyond one year, remain disappointingly low for such an invasive procedure. In fact, Pison et al. reported on their experience with such a procedure, with a success rate of 83% at one year follow up without continuous monitoring with inclusion of PAF patients. Success rates for these procedures may be tempered by edema introduced during the surgical approach which limits electrophysiological mapping either simultaneously or shortly thereafter; thus, resulting in areas of extensive tissue edema masquerading as true transmural lesions. In addition, critical areas of arrhythmogenesis may be precluded from appropriate mapping and/or ablation. Krul et al. describe a success rate of 75% at one year (no continuous monitoring was performed) in persistent AF using a real-time mapping approach that required customized equipment or a hybrid EP lab, which are not widely available.

We propose that the success rate of a hybrid atrial fibrillation ablation procedure can increase for both persistent AF (PeAF) and long-standing persistent AF (LSPeAF) by having the endocardial approach precede the surgical approach, which most centers should be able to perform. The endo-before-epi surgical hybrid AF ablation procedure is defined by a comprehensive endovascular approach preceding and guiding the epicardial ablation coupled with an extensive epicardial posterior wall ablation to replace the posterior “box lesion” and mitral isthmus lines and their resulting proarrhythmia.

**Baseline Characteristics**

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Percentage (%) or Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male = 70.0%</td>
</tr>
<tr>
<td>Age (Years)</td>
<td>61.7 ± 7.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.3 ± 6.8</td>
</tr>
<tr>
<td>AF Type</td>
<td>Persistent = 77.5%</td>
</tr>
<tr>
<td></td>
<td>Long-standing persistent = 22.5%</td>
</tr>
<tr>
<td>AF Duration (Years)</td>
<td>6.0 ± 4.5</td>
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<tr>
<td>Mitral Regurgitation</td>
<td>Mild = 52.2%</td>
</tr>
<tr>
<td></td>
<td>Moderate = 42.5%</td>
</tr>
<tr>
<td></td>
<td>Severe† =5.0%</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>55.7 ± 5.7</td>
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<tr>
<td>LA Size (cm)</td>
<td>4.7 ± 0.8</td>
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<tr>
<td>LA Volume (cc)</td>
<td>131.5 ± 46.9</td>
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<tr>
<td>Comorbidities</td>
<td>Diabetes = 17.5%</td>
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<tr>
<td></td>
<td>Hypertension = 80.0%</td>
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<tr>
<td></td>
<td>Obstructive sleep apnea = 55.0%</td>
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<tr>
<td># of AADs Tried</td>
<td>1.55 ± 0.7</td>
</tr>
<tr>
<td>Prior ablation</td>
<td>Yes = 22.5%</td>
</tr>
</tbody>
</table>

**Table 1. Baseline Characteristics**

AAD: Antiarrhythmic drug  
AF: Atrial fibrillation  
BMI: Body Mass Index  
LVEF: Left ventricular ejection fraction  
LA: left atrium  
†: Refused open procedure

**METHODS**

**Study Design and Population**

The study was designed as a prospective observational study with 40 patients being enrolled between January 2012 and December 2014. The study was approved by the St. Vincent’s Hospital Institutional Review Board and all patients gave informed consent. All patients had persistent or long-standing persistent AF, were highly symptomatic and had previously failed medical management with a class I or class III antiarrhythmic medication. Patients were chosen for the hybrid procedure if they were considered to be predisposed to a less efficacious outcome from a standard endocardial procedure based on one of the following criteria: (1) persistent AF with failure of antiarrhythmic drug therapy, (2) persistent AF with large left atrial size (> 90 mL) by CT scan or concomitant structural heart disease, (3) long-standing persistent AF, and (4) prior failed endocardial ablation. Refer to table 1 for patient characteristics. Patients greater than 18 years of age undergoing the hybrid AF procedure at St. Vincent’s Medical Center Bridgeport, Connecticut were included in this study. Exclusion criteria included: pregnancy, incarceration, severe valvular disease or other cardiac indication for an open procedure and mechanical valves. Procedural complications were predefined as life-threatening or disabling complication or those requiring additional hospitalization for observation (stroke, systemic or pulmonary embolism, esophageal injury other than esophagitis, phrenic nerve injury, symptomatic pulmonary vein stenosis, pericardial effusion with or without tamponnade, groin complications, major bleeding) occurring within 30 days of the procedure.

**Preoperative Care**

For patients anticoagulated with warfarin, warfarin was discontinued five days before the endocardial procedure. Epicardial procedures were performed with INR of 1.7 or less. If the patient was taking a novel oral anticoagulation agent (NOAC), the NOAC was discontinued 12-48 hours prior and resumed the day after the epicardial procedure. High-risk patients, including those with prior cerebrovascular accident or hypercoagulable states, were bridged with enoxaparin prior to the procedure. If not already prescribed, an antiarrhythmic drug (AAD) was initiated, amiodarone being the drug of choice if tolerated. After oral AAD load, an attempt at restoration of sinus rhythm was performed with one direct current cardioversion. If early recurrence of AF was noted, further attempts at restoration were deferred prior to the hybrid AF procedure. All patients underwent pre-procedural cardiac computer tomography evaluation to delineate the left atrium and pulmonary vein anatomy.

**Endovascular Approach**

The procedure is performed over two consecutive days. The endocardial approach was standardized and performed by a single operator. All patients receive a transesophageal echocardiogram to evaluate for intracardiac thrombus as well as other structural abnormalities for repair of which sternotomy would be required, at which time an open surgical Cox Maze procedure could be performed. General anesthesia is used
throughout the endovascular approach with the esophageal temperature being monitored with a single sensor esophageal temperature probe placed under fluoroscopy. Venous access is performed at both the right and left femoral veins and once access is established, 3000 to 5000 units of heparin is administered. A duodecapolar catheter (St. Jude Medical, St Paul, MN) is placed along the lateral right atrial all and into the coronary sinus via the femoral vein. A 10 Fr intravascular ultrasound catheter (St. Jude) is then placed in the right atrium to aid in performing transeptal puncture, guiding catheter location and monitoring for any cardiac complications. A 5.0-6.0 Fr quadripolar diagnostic catheter is advanced to the right ventricular apex for pacing and sensing. With a St Jude steerable sheath positioned at the interatrial septum, a single transeptal puncture is performed with the use of a Brockenbrough-1 needle under fluoroscopic and ultrasound guidance. Additional heparin is then administered with continual infusion and activated clotting time monitored with a goal of > 350 seconds via intraprocedural iStat (Abbot, Princeton, New Jersey) monitoring.

With the use of the St. Jude Velocity Ensite-Precision mapping system and a 20-pole circular catheter, an electro-anatomical map of the left atrium and pulmonary veins is created. If the patient presented in atrial fibrillation, complex fractional atrial electrograms are also mapped during the anatomical mapping of the left atrium.

Endovascular lesion sets are then applied with radiofrequency ablation with a St. Jude irrigated bidirectional ablation catheter. Wide area circumferential ablation with carinal lesions (if accessible) is performed around all pulmonary veins. A power cutoff of 30 watts and 15 watts is utilized along the anterior and posterior walls respectively. If a temperature rise in the esophagus greater than 0.2 degrees is seen, the radiofrequency ablation is discontinued in the area. A roof line is placed connecting the upper pulmonary veins along a posterior course as anatomically allowed. Integrity of the roof line is verified by changes in activation of the coronary sinus catheter compared to baseline and presence of split potentials along the line. Ablation of pre-procedural documented atrial tachycardias is then performed if deemed clinically relevant. Further lesions are then applied at the mapped complex fractionated electrogram (CFAE) sites. Confirmation of isolation of all pulmonary veins is then performed by demonstrating entrance and exit block with a St. Jude circular duodecapolar catheter. Adenosine and/or isoproterenol were not routinely used. If atrial fibrillation persists despite these lesion sets, typically no electrical cardioversion is performed to reduce the risk of post operative cerebrovascular accident while awaiting the epicardial approach.

Once isolation of all pulmonary veins and integrity of roof line has been confirmed, catheter and sheaths are withdrawn from the left atrium. Once within the right atrium, a cavo-tricuspid isthmus ablation line is performed regardless of whether or not atrial flutter has been previously observed. In addition, lesions are applied along the coronary sinus os. Once completed, heparin is then reversed with protamine and sheaths are removed from the femoral vein with manual compression utilized for hemostasis. Implantable loop recorders were then placed in all patients to allow for continuous cardiac monitoring after discharge.

Epicardial Approach

The epicardial approach is performed on day two also under general anesthesia. The electrophysiologist was present in the room to direct application of lesions based on available EnSite maps from the endocardial procedure. A double-lumen endotracheal tube is utilized for selective lung ventilation and a tranesophageal echocardiography probe as well as an esophageal temperature probe is in place throughout the surgical approach. Surgery is started on the patient’s right side after deflation of the right lung and with placement of three ports. Dissection is then performed to the pericardium with focus on localizing the phrenic nerve and esophagus. Right-sided ganglionated plexi (GP) are localized by burst pacing. If a “vagal response” is provoked, radiofrequency ablation is performed in this area. The right-sided pulmonary veins are then clamped utilizing the AtriCure ablation clamp (Atricure, Mason, OH) and further dissection is performed posteriorly. An AtriCure linear pen is utilized to ablate within the posterior left atrial wall as well as initiating the first-half of a roof line connecting the upper pulmonary veins. Focus is then turned to ablating areas that posed difficulties from an endovascular approach due to anatomy or safety. Further epicardial lesions are applied in areas of endovascularly-mapped CFAE regions as well as any clinically relevant sites of atrial tachycardia that were previously localized. After direct visualization of re-inflation of the right lung, ports are removed and access points are closed. Attention is then directed to the left side. Similarly, after deflation of the left lung, 3-4 ports are placed. Further dissection is then performed posteriorly. The ablation pen is further utilized to complete lesion sets to the posterior wall and finish the roof line as well as to complete lesions to further GPS and prior mapped sites that proved difficult via endovascular approach. The vein of Marshall is then localized and dissected from the left atrium. Ablation is performed within the ridge of the appendage. The posterior wall between the roof line and the mitral isthmus is completely ablated. Once ablations are completed, attention is turned to left atrial appendage closure using the AtriCure Atriclip.

Termination of atrial fibrillation is not a procedural endpoint and once the procedure is deemed complete, if atrial fibrillation persists, direct current cardioversion is applied to restore sinus rhythm. The left lung is then reinflated under direct visualization, ports removed and the left side closed. Mitral isthmus lines are not performed.

Post Operative Care

Oral anticoagulation is continued in all patients post conversion to sinus rhythm for at least 3 months. Thereafter, continuation of anticoagulation agent is determined by the patients’ overall risk (CHADS-VASc score),^{14,15} bleeding risk and patient preference.
The epicardial approach was able to be performed within 24 hours in 85% of patients. Left atrial appendage closure with the Atriclip was performed in 37/40 (92.5%). There were no procedural complications within 30 days and no patients required conversion to an open surgical procedure for completion of the procedure. Implantable cardiac monitoring (ICM) was in place (either with a newly placed ILR or prior implanted permanent pacemaker or defibrillator) in all patients at procedure completion. Oral antiarrhythmic agents were discontinued following an approximate three month blanking period after the procedure.

Findings
Follow up for 12 months was performed in all 40 patients.

At one year follow up all 40 patients with previously diagnosed persistent and long-standing persistent atrial fibrillation were documented to be in sinus rhythm. While atrial arrhythmias were seen, these were paroxysmal in nature. Freedom from recurrence of any atrial arrhythmia was seen in 35/40 patients (87.5%) outside the 3 month blanking window.

Freedom from recurrence of atrial arrhythmias trended higher in patients with documented persistent atrial fibrillation vs. long standing atrial fibrillation prior to the procedure, although this difference did not reach statistical significance. Despite this finding, maintenance of sinus rhythm on follow-up was documented in all patients (Table 3).

DISCUSSION
While endocardial catheter ablation has been well established in the management of paroxysmal atrial fibrillation, its success in persistent atrial fibrillation has been limited. This is likely due to a dynamic continuum of structural, electrical and contractile remodeling.18 Better understanding of underlying pathophysiology has led to a better understanding of anatomical targets and advancements in technology have improved the available tools for performing minimally invasive procedures. We can now apply effective epicardial and endocardial lesions
In a combined approach leading to the development of hybrid procedures incorporating epicardial lesion sets along with catheter-based endocardial approaches. Utilizing a hybrid approach to atrial fibrillation allows transmural, complete lesions and lesion sets can be completed in areas difficult to approach from an endocardial aspect alone when combining a minimally invasive epicardial approach with additional safety when applying lesions near the right phrenic nerve or esophagus.

In this report, we describe a novel approach to the hybrid AF ablation, utilizing a comprehensive endovascular approach preceding and guiding the epicardial ablation that was created in response to the challenge of non-PAF and as a collaborative approach to optimize each approach’s strengths and overcoming the logistic difficulties of real-time intraoperative mapping. The endovascular approach was often met with anatomic complexities or large areas of arrhythmic substrate that could not be addressed with an endovascular approach alone, therefore resulting in recurrent atrial arrhythmias after multiple such procedures. By using the electrophysiology study and ablation to guide, direct and tailor the epicardial approach, 87.5% of patients with either persistent or long-standing persistent AF were free of atrial arrhythmias at one year, as documented with continuous monitoring, and all documented events were noted to be paroxysmal in nature requiring no re-intervention. This success rate validates the utility of a “reverse” hybrid approach (an endovascular guided epicardial approach) for the management of persistent and long-standing persistent atrial fibrillation.

Literature has shown that there can be multiple extra-pulmonic vein sources of initiation and maintenance of AF with the most common sites including the superior vena cava, ligament of Marshall, coronary sinus, crista terminalis, and left atrial posterior wall.19,20 The lesion set performed in this approach is systematic and certainly comprehensive which attributes to the high success rates.

The posterior left atrial wall is highly arrhythmogenic with a high concentration of fibrosis with heterogeneity of conduction properties with sites of fast-organized activity and high incidence of dominant frequencies.18,21 However, attempts at isolation of the posterior wall have proven difficult with either endocardial or epicardial alone since the gaps in the lines are arrhythmogenic. In an answer to this challenge, a multidisciplinary approach utilizing pericardioscopic convergent procedure to epicardially segment the posterior left atrium has garnered improved success rates.12,22,23 We utilized the improved pericardial access via a thoracoscopic approach to perform a comprehensive segmentation of the left atrial posterior wall along with other substrate modification. This allowed us to successfully isolate the pulmonary veins and silence the posterior left atrium, resulting in superior clinical results.

The autonomic ganglionated plexi (GP) have also been shown to likely contribute to the perpetuation of the AF substrate. GPs are anatomically located along the ligament of Marshall, the great vessels, at the right superior pulmonary vein (PV)-atrial junction, at the left superior PV-atrial junction, at the left inferior PV-atrial junction, and at the junction of the inferior vena cava. Direct stimulation of GPs trigger pulmonary vein ectopy and perpetuate atrial fibrillation by reduction of PV sleeve action potential duration, and shortening of the fibrillation cycle length.24 Thus, we systematically performed GP mapping with ablation as this significantly increases success rates in patients with non-PAF.25

Another strength of the described procedure is that it addresses the often ignored arrhythmogenic regions in the non-PAF heart such as the ligament of Marshall (LOM), left atrial appendage (LAA) and coronary sinus with its inter-atrial musculature sleeves. The LOM contains parasympathetic and sympathetic nerve fibers along with Marshall bundles that insert into the LA free wall and CS forming connections and substrate for reentrant excitation.26 In addition, the anatomical proximity of the LOM to the sympathetic nerves may provide a mechanism for adrenergic atrial tachyarrhythmia in humans. Thus, we directed our lesion set to the LOM by having the surgeon perform a LOM dissection; furthermore, LAA clipping likely modified the remaining LOM as well by mechanical disruption. The LAA is under-recognized and under-addressed as potential substrate for initiating and maintain atrial fibrillation, particularly with redo ablations as depicted by DiBlase et al.27 This was suggested in our small database when we saw five patients terminate their AF with LAA clipping. We believe that the LAA clipping provides both a thromboembolic and an electrophysiologic benefit.
As to the coronary sinus, there is the clear presence of histologic-anatomic connections linking the inferior right atrium to the left atrial myocardium via a cuff of striated muscle around the coronary sinus in humans. 28 Overall, the presence of these variable muscular connections indicates a consistent pathway for interatrial propagation and possibly further reentrant flutters if not addressed. We feel we addressed this potential short-fall by incorporating a CS os lesion set into the cavotricuspid isthmus line.

It was also noted that overall procedure time was able to be reduced with adoption of the herein-described hybrid approach. This decrease in procedure time was noted in both the endocardial as well as the epicardial portions of the procedure.

The strengths of this study are that it represents a single-center study where the lesion-application strategy was uniform amongst all patients. It also shows an excellent one year arrhythmia-free survival even when accounting for the continuous monitoring strategy, the inclusion of very dilated left atria and the exclusion of patients with paroxysmal atrial fibrillation.

CONCLUSION

We describe promising results at 12 months in PeAF and LPeAF patients using a hybrid approach wherein the endovascular lesions are applied prior the epicardial compared to the traditional approach of epicardial lesions first compared to previously described reports and with higher success rates than in these same reports. All recurrent arrhythmias were paroxysmal in nature and required no intervention for management. Although clearly establishing the superiority of this approach would require a randomized trial, we believe it shows enough promise to warrant further investigation and longer-term data.

REFERENCES


**Joseph J. Tiano, MD** is affiliated with St. Vincent’s Medical Center, Bridgeport, Connecticut 06824; **Robert Drennan, MD**, is affiliated with the Louisiana State University Health Sciences Center – New Orleans, 433 Bolivar St, New Orleans, Louisiana, 70112; **John Novella, MD**, is affiliated with St. Vincent’s Medical Center, Bridgeport, Connecticut 06824; **Rafael Squiteri, MD**, is affiliated with St. Vincent’s Medical Center, Bridgeport, Connecticut 06824; **Malcolm Robinson, MD**, is affiliated with St. Vincent’s Medical Center, Bridgeport, Connecticut 06824; **Albert DiMeo, MD**, is affiliated with St. Vincent’s Medical Center, Bridgeport, Connecticut 06824; **Lindsey Scierka, MPH**, is affiliated with Quinnipiac University, Hamden, Connecticut, 06511; **Paul LeLorier, MD**, is affiliated with Louisiana State University Health Sciences Center – New Orleans, 433 Bolivar St, New Orleans, Louisiana, 70112.
A 57-Year-Old Man with an Axillary Mass

Palak Desai MD, Andrew Myers, Brian Boulmay MD, Fred A. Lopez MD

A 57-year-old man presented to the surgical oncology clinic with a mildly tender mass under his right arm. Four years prior, the patient had a melanoma removed from his right shoulder along with an ipsilateral right axillary sentinel lymph sampling. Computed tomography (CT) scan was negative for metastatic disease at that time. The patient did not undergo completion axillary node dissection and was lost to follow-up. The patient was originally from Australia, did not tan but reported multiple sunburns before age 18. He was of Irish ancestry. He denied weight gain, fever, fatigue, anorexia, or night sweats.

The patient had a medical history of atrial fibrillation, hypertension, gout, melanoma, and benign prostatic hypertrophy. His surgical history included an appendectomy and a facial laceration repair. His brother died at 16 years old from leukemia and his mother died from colon cancer. He consumed 3 alcoholic beverages per day and denied tobacco or illicit drug use.

On physical exam, the patient’s temperature was 98.8° Fahrenheit, heart rate of 73 beats / minute, blood pressure of 121 / 59 mm Hg, respiratory rate of 18 / min. He appeared to be healthy and in no apparent distress. Cardiovascular, respiratory, breast, gastrointestinal, musculoskeletal, and neurological exam were unremarkable. His right axillary lymph node exam revealed a firm mass roughly 2.5 cm tall by 1.5 cm wide. This mass was biopsied and findings were consistent with metastatic melanoma. CT scan revealed small volume mediastinal adenopathy and a 4.5 cm right axillary mass. There was a 4.7 cm lesion within the anterior left lower lobe of the liver and periportal node conglomerate measuring 3.9 cm consistent with metastatic disease (Figure 1). He was negative for the BRAF V600E mutation.

The patient was consented for treatment with combination immune checkpoint inhibition with ipilimumab and nivolumab. After two cycles the patient showed good response, but temporarily stopped treatment after complications related to a ST segment elevation myocardial infarction. He developed mild pneumonitis felt to be related to nivolumab, and recovered after a short course of glucocorticosteroids. Restaging CT scans were ordered after two cycles of therapy (Figure 2), which showed decrease in the size of the axillary and hepatic metastases. At six months, CT scans showed continued durable response (Figure 3).

Figure 1. Prior to initiation of Immunotherapy, the patient was found to have a 4.5cm R axillary mass as well as a 4.7 cm liver mass (in red circles)

Figure 2. After two cycles of nivolumab and ipilimumab, both the patient’s axillary and liver masses decreased in size
EPIDEMIOLOGY

Melanoma is a life threatening form of skin cancer that is most commonly associated with excessive ultraviolet light exposure. It affects roughly one million Americans and is projected to claim over 10,000 lives in 2016.1 Stage IV, or metastatic melanoma, is thought to be incurable.2 Historically, alkylating chemotherapy agents such as dacarbazine and temozolomide have been used with limited efficacy.3,4 Interferon-α2b (IFN-α2b) and high dose interleukin-2 (IL-2) therapy were mainstays in the treatment of metastatic melanoma; surgical resection is reserved for cases of limited metastatic tumor.5

Advances in tumor genomics have recently improved survival rates in patients with metastatic melanoma. For example, a mutation of BRAF is found in half of all melanomas: the V600E BRAF mutation causes unregulated cell proliferation via the MAP kinase pathway.6,7 Metastatic melanomas positive for BRAF mutation can be treated with the BRAF inhibitors, vemurafenib or dabrafenib, and can result in a relative reduction of death by 63%.3,6 Concurrent inhibition of the BRAF and MEK of the MAP kinase pathway can result in a higher rate of tumor responses and longer duration of responses. Treatment with the MEK inhibitor trametinib combined with dabrafenib has been shown to have an objective response of 76%, with a median progression free survival (PFS) of 9.4 months vs 5.8 months for patients who received dabrafenib monotherapy alone (HR 0.39, P<0.001).7

RATIONALE FOR IMMUNOTHERAPY

Recent advances in immunotherapy have provided patients with more durable responses and longer survivals. Metastatic melanomas with and without BRAF mutations may be treated by new immune checkpoint inhibitors, such as nivolumab (anti-PD1 antibody) and ipilimumab (anti-CTLA4 antibody), used in our case patient.

Historically, traditional cytotoxic chemotherapy produced modest benefit. For example, dacarbazine resulted in a low response rate (10-15%) and an overall survival (OS) of eight months.8 Interestingly, the immune mediating cytokines also were shown to result in some long-term objective response rates in a limited number of patients. These results suggested that melanoma could be an ideal target for immune manipulation. But, the crude, non-targeted nature of these therapies often resulted in unacceptable toxicities for many patients.

Developments in the understanding of the tumor micro-environment allowed for the ultimate development of more targeted immune mediating drugs. Melanomas are often found to contain tumor-infiltrating lymphocytes (TIL). These cytotoxic T-lymphocytes (CTL) are capable of inducing tumor cell lysis and studies in the 1980s demonstrated the ability of IFN-2 to mediate these cells to cause tumor regression in melanomas.9,10 Tumors infiltrated with T cells were found to have better long-term patient survival. The mechanism behind a response was thought to be secondary to an active antitumor response by the patient’s immune system. This discovery led to therapeutic approaches using recombinant high-dose IL-2 to induce immune-mediated tumor cell lysis in patients with metastatic melanoma.9 Several studies demonstrated objective responses in 10-16% of patients treated with high dose IL-2.10 However, high dose IL-2 treatment is associated with severe toxicity such as vascular leak syndromes, requiring inpatient management. While these factors have limited its generalized use, high dose IL-2 served as proof-of-principle that immunotherapies can be effective.

When grown ex-vivo, TILs exhibit potent antitumor activity. However, in patients, TILs often have a diminished capacity for proliferation, tumor lysis, and cytokine production.11 This implies that the immune climate within the tumor micro-environment (TME) can dampen CTL activity, the result being limited efficacy of IFN-α2b and IL-2. Understanding of the micro-environment has led to the expansion of today’s drug armamentarium.

INHIBITION OF CTLA-4

One mechanism by which T-cells self-regulate is through expression of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), a receptor found only on T cells. It functions as a negative co-stimulatory molecule for the T cell.12 CTLA-4 binds to CD80 and CD86 on antigen-presenting cells and by outcompeting CD28 for binding to CD80 and CD86, CTLA-4 can present the co-stimulation needed to maintain T-cell activation (Figure 4).13

Ipilimumab is a fully human IgG-1 monoclonal antibody that blocks CTLA-4, resulting in increased T-cell activity and promoting antitumor activity.14 Two phase-III trials have evaluated ipilimumab in the treatment of metastatic melanoma.14,15 In the first trial of patients with treated unresectable stage III or IV melanoma, ipilimumab demonstrated an improved OS versus
glycoprotein-100 peptide vaccine (10.1 vs 6.4 months).

The impressive findings from this study were the one and two year OS rates for the ipilimumab arm: 45.6% and 23.5% respectively. Similar rates were seen in the combination arm. The 1-year OS rate was higher than any other experimental regimen for patients with metastatic melanoma. In the second phase III trial, previously untreated patients with metastatic melanoma were treated with ipilimumab plus dacarbazine versus dacarbazine alone. The combination group median OS was superior to the dacarbazine alone group (11.2 vs 9.2 months). In both phase III trials, the response rate was only 10-15% and the disease control rate (complete response, partial response, and stable disease) was 30%. Pooled analysis of 10 prospective and two retrospective studies of ipilimumab as monotherapy in patients with advanced melanoma showed a three year OS of 22%. A substantial number of patients in both trials continued to have long disease control more than five years after completion of therapy.

**INHIBITION OF PD-1**

Programmed cell death ligand 1 (PD-L1) is expressed by many cells to induce immune tolerance. The interaction between PD-L1 with the programmed cell death protein 1 (PD-1) receptor on CTLs leads to immune tolerance by causing apoptosis of the T cell. So, for example, melanoma cells expressing PD-L1 on the tumor surface can evade host immune response through this down regulation. Antibodies directed against PD-1 or PD-L1 would be expected to block the down regulatory signal of the tumor and restore antitumor immunity within the tumor microenvironment (Figure 5).

Clinical activity of the anti-PD-1 monoclonal antibody nivolumab has been shown to result in OS rates of 62% at 1 year, 43% at two years, and 41 percent at three years. Data presented at the 2016 American Association for Cancer Research (AACR) Annual Meeting showed a robust five year OS of 34% for patients with advanced melanoma treated with nivolumab. The study population had never been treated with ipilimumab and had received between one and five prior therapies for their disease.

Nivolumab has been studied as a second line setting. The Checkmate-037 trial randomized nivolumab versus investigator’s choice chemotherapy in patients with advanced melanoma whose disease had progressed after ipilimumab and a BRAF inhibitor administration if the tumor contained a BRAF V600 mutation. The study showed a superior overall response rate (ORR) in the nivolumab group of 31.7%, compared to an ORR of 10.6% in the chemotherapy arm.

Nivolumab has also been studied head-to-head with ipilimumab in patients with metastatic melanoma, in the first-line setting. Checkmate-067 was a randomized phase III trial comparing ipilimumab to nivolumab in patients with advanced melanoma who were naïve to immunotherapy. The ORR was 43.7% with nivolumab compared to 19.0% with ipilimumab. Nivolumab also had a longer PFS (HR, 0.57, P<0.001).

A second PD-1 inhibitor, pembrolizumab has shown substantial activity in metastatic melanoma. Pembrolizumab’s strong clinical activity was first seen in the phase-1 KEYNOTE-001 trial where pembrolizumab was shown to produce durable responses in both ipilimumab-naïve and previously treated patients with melanoma with an ORR of 33%. KEYNOTE-002 was a phase II trial comparing pembrolizumab to physician’s choice of chemotherapy in patients with advanced melanoma. Superior clinical activity was seen in the pembrolizumab group with an ORR of 25% vs 4% in the chemotherapy arm. Median PFS was 5.6 months vs. 3.6 months in the pembrolizumab and chemotherapy arms, respectively. OS was similar, however, crossover from the chemotherapy to pembrolizumab arms was permitted, making OS assessments difficult.

Like nivolumab, pembrolizumab has also been studied head-to-head with ipilimumab. The Phase III study KEYNOTE-006 compared pembrolizumab versus ipilimumab in patients with melanoma who were naïve to immunotherapy. ORR was higher...
in the pembrolizumab arm, 33.7% vs. 11.9%. The 6-month PFS rates were 47.3% in the pembrolizumab arm vs 26.5% in the ipilimumab arm.

The data from KEYNOTE-006 and Checkmate-067 confirm the clinical superiority of anti-PD-1 therapy versus anti-CTLA-4 therapy in patients with metastatic melanoma.

Checkmate-067 was a three arm, double blind, phase III trial that randomized patients to nivolumab alone, nivolumab plus ipilimumab followed by nivolumab maintenance, or ipilimumab alone. The median PFS in the combination group was 11.5 months compared to 2.9 months in the ipilimumab group and 6.9 months in the nivolumab alone group. The results from Checkmate-069 and Checkmate-067 studies show that the combination of ipilimumab and nivolumab produces impressive antitumor activity.

The data from KEYNOTE-006 and Checkmate-067 confirm the clinical superiority of anti-PD-1 therapy versus anti-CTLA-4 therapy in patients with metastatic melanoma.

The data from KEYNOTE-006 and Checkmate-067 confirm the clinical superiority of anti-PD-1 therapy versus anti-CTLA-4 therapy in patients with metastatic melanoma.

**IMMUNOTHERAPY TOXICITIES**

Despite immunotherapy’s benefits, treatment with checkpoint inhibitors is associated with a unique spectrum of side effects termed immune-related adverse events (IrAEs). The most common IrAEs reported have been arthralgia, nausea, diarrhea, fatigue, pruritis, rash, and hypothyroidism. Severe cases of colitis, dermatitis, pneumonitis, and hepatitis have been reported in 1% or less of patients. IrAEs of any grade with ipilimumab occur in the majority of patients, as seen in 64.2% of patients in a pooled analysis of 14 phase I–III studies of ipilimumab. Most toxicities are mild to moderate (grade 1–2), involve mainly skin and GI events. Furthermore, the incidence and severity of ipilimumab toxicities appear to be dose related. The rates of severe events (grade 3-5) in anti-PD-1 therapy have been lower than those seen with ipilimumab, occurring in 14% of patients treated with either pembrolizumab or nivolumab. Optimal management of IrAEs includes the early recognition and the appropriately timed use of immunosuppressive agents, such as steroids or anti-TNF-α drugs, based on the severity of the event.

**DISCUSSION**

The development of checkpoint inhibitor immunotherapy has significantly changed the treatment landscape of advanced melanoma treatment. Anti-CTLA-4 and anti-PD-1 based therapies can produce response rates of above 50% and have been proven to be safer and more effective than traditional therapies such as systemic IL-2. Historically metastatic melanoma has been associated with a poor prognosis, with a median OS of 8-10 months, and a five-year survival of 10%. Immunotherapy has shown to significantly prolong the PFS as well as show a durable response with a 34% five-year response rate for nivolumab monotherapy. Harnessing the body’s immune system to target tumor cells is an effective and relatively safe approach to treating such an aggressive disease. As other promising immunotherapies for melanoma proceed through clinical trials, the more we will begin to understand the natural course of melanoma and the interaction between the body’s immune system and tumor cells. This understanding will ultimately lead to more treatment options for our patients, and ultimately longer survivals for those affected by advanced melanoma.
REFERENCES


Dr. Desai is a third-year fellow at the LSUHSC in the Section of Hematology/Oncology; A. Myers is a second-year medical student at the LSU School of Medicine, New Orleans; Dr. Boulmay is an Associate Professor in the Section of Hematology/Oncology at LSUHSC-New Orleans; Dr. Lopez is the Richard Vial Professor and Vice Chair in the Department of Medicine at LSUHSC- New Orleans, LA.
ECG CASE OF THE MONTH

Chest Pain and ECG Abnormalities

D. Luke Glancy, MD

A 27-year-old man was admitted to the coronary care unit because of chest pain and an electrocardiogram (ECG) read by the computer as an inferior infarct and left ventricular hypertrophy (Figure).

Figure 1. Electrocardiogram in a 27-year-old man with chest pain. See text for explication.

What is your diagnosis?

Explication is on p. 84.
DIAGNOSIS

The short PR interval (0.10 seconds), wide QRS complex (0.12 seconds), and delta waves (best seen in leads II, III, aVF, V1, V3-V6), are features of ventricular preexcitation of the Wolff-Parkinson-White type (WPW).¹

WPW is a notorious mimic of other conditions, especially myocardial infarct and left ventricular hypertrophy. WPW is best known for its association with supraventricular tachycardias which are usually initiated by an atrial premature complex, but can be initiated by ventricular premature complexes. The ensuing atrioventricular reciprocating tachycardia has a reentrant circuit usually characterized by so-called orthodromic conduction down the atrioventricular node, His bundle, and bundle branches, i.e., the normal conduction pathways, with conduction back to the atria via the accessory pathway, and the QRS complex is usually narrow unless the patient has a coexisting bundle branch block.¹ In a minority of cases, conduction is antidromic, i.e., down the accessory pathway with return to the atria retrogradely via the normal conduction system. Under these circumstances, the QRS complex is wide and not typical of block in either bundle branch. Not all patients with WPW-type ventricular preexcitation have tachyarrhythmias,² and thus far this patient has no history of same.

REFERENCES


Dr. Glancy is an emeritus professor of medicine (cardiology) at the Louisiana State University Health Sciences Center in New Orleans, LA.
Idiopathic CD4 Lymphocytopenia

Chris Malone, BS, Neel D Gupta, MD, Amit Kothari, MD, Enrique Palacios, MD, Harold Neitzschman, MD

A 39 year-old male with a history of diabetes, retinitis pigmentosa, and genital warts presented with intractable occipital headaches accompanied with nausea and vomiting. The patient had markedly depressed CD4 counts. Furthermore the patient tested negative for HIV and HTLV 1/2 and had normal immunoglobulin levels. During hospital course the patient underwent a lumbar puncture and multiple imaging exams, including both CT and MR. Except for occasional nausea and vomiting controlled by therapeutic lumbar punctures, phenergan, and dilaudid the patient's hospital course was uncomplicated.

Figure 1a. Axial FLAIR image

Figure 1b. Axial T2 Weighted Image

Figure 1c. Axial T1WI with contrast

Figure 2a. Sagittal T1WI with contrast

Figure 2b. Axial T1WI with contrast
Idiopathic CD4 Lymphocytopenia with Cryptococcal Meningitis and Cryptococcal Abscess

INTERPRETATION OF IMAGES

MR (Figure 1A) axial FLAIR image demonstrates abnormal signal intensity within the left caudate nucleus. (Figure 1B) axial T2WI demonstrates dilatation of perivascular spaces at the base of the brain. (Figure 1C) axial T1W post contrast demonstrates enhancement of a necrotic lesion involving the head of the caudate nucleus. (Figure 2A) and (Figure 2B) reveal enhancement of the leptomeninges over the cerebellum.

DISCUSSION

Idiopathic CD4 Lymphocytopenia (ICL) is a rare immunodeficiency characterized by low CD4 counts in the absence of human immunodeficiency virus (HIV) and other immunodeficiencies. The most common presenting opportunistic infection in patients with Idiopathic CD4 Lymphocytopenia (ICL) is cryptococcal meningitis followed by persistent genital manifestations of human papilloma virus (HPV). Patients may also suffer from tuberculosis and other atypical mycobacterial infections. Previous cases have shown patients with this disorder suffering from a wide variety of opportunistic infections including Pneumocystis jiroveci pneumonia, aspergillosis, toxoplasmosis, histoplasmosis, hepatitis C, Epstein barr virus (EBV), cytomegalovirus (CMV), John Cunningham (JC) virus, and Fusobacterium nucleatum. Mainstay therapy includes prophylaxis according to HIV guidelines for certain CD4 count thresholds and treatment of any opportunistic infections.

This condition is defined by the presence of persistent CD4 lymphocytopenia in the absence of HIV infection, and should be considered a diagnosis of exclusion when other conditions leading to depressed CD4 counts are ruled out. Specific criteria for diagnosis include CD4 cell counts below 300 cells/ml or less than 20% of total lymphocytes on at least 2 separate analyses. Any other immune deficiency due to underlying condition or drugs must be excluded. This includes common variable immune immunodeficiency (CVID), which presents with low immunoglobulin levels. Other laboratory findings are variable but may include a slightly elevated or normal CD8 count, CBC differential demonstrating lymphopenia, and normal or slightly low immunoglobulin levels. ICL is distinguished from HIV in that HIV is associated with elevated counts of immunoglobulins and an early elevated CD8 count. Theories behind the pathogenesis include diminished generation of T-cell precursors, increased T-cell apoptosis, alteration of p56 Lck kinase resulting in a defunct CD3 T cell receptor pathway, defective production of cytokines, and circulating CD4 T-cell antibodies.

Cerebrospinal fluid (CSF) in our patient obtained by lumbar puncture from an outside facility grew Cryptococcus neoformans, diagnosing the patient with Cryptococcus meningitis. The patient had CD4 counts of 54 and 72 on two separate measurements during the course of his stay, which fulfilled criteria for diagnosis of Idiopathic CD4+ Lymphocytopenia (ICL). An initial MR of the patient’s brain from an outside facility showed an area of abnormal restricted diffusion in the left caudate nucleus on diffuse weighted imaging (DWI) with corresponding abnormality on apparent diffusion coefficient (ADC) map respectively, consistent with a recent vascular insult or inflammatory process. The patient was started on both Amphotericin B at 5 mg/kg and fluconazole 400 mg daily. A repeat lumbar puncture was performed during patient’s inpatient treatment, which revealed 48 protein, 87 glucose, 45 WBC (98 lymph, 2 mono), and 3 RBCs. The cerebrospinal fluid obtained (CSF) was positive for India ink stain and showed a cryptococcal antigen titer of 1:512.

In our patient, it appeared that the meningeal component of the Cryptococcal infection involved the perivascular spaces at the base of the brain and cerebellar leptomeninges. On magnetic resonance (MR), there was a focal hyperintensity, with abnormal restricted diffusion indicating acute insult. This was consistent with Cryptococcal involvement of the basal ganglia secondary to Cryptococcal meningitis by way of the perivascular spaces. Patients with AIDS often demonstrate a wide spectrum of cryptococcal manifestation patterns on MR, with dilated perivascular Virchow-Robin spaces. As the infection spreads along these perivascular spaces, these spaces may become increasingly dilated and become filled with mucoid and gelatinous material produced by the organism’s capsule. In addition, enhancing parenchymal lesions are a sign of further invasion from the CSF spaces forming a granulomatous process as was noted with our patient. Ventricular dilatation, leptomeningeal enhancement, and cryptococcomas are common findings on MR. However dilatation of Virchow-Robin spaces tend to be the common finding and should raise concern for cryptococcal infection in any immunocompromised patient.

A follow up with MR of the brain was performed in our patient 18 days after admission, which showed the area of the left caudate nucleus as a ring-enhancing abscess (Figure 1C). The areas of scattered enhancement at the base of the brain and meninges appeared more prominent. As the patient was maintained on Amphotericin B and fluconazole therapy during his treatment period, these areas of abnormal enhancement and rim-enhancing abscess in the left caudate nucleus decreased in size. MR spectroscopy was performed in order to evaluate the area of the left caudate nucleus considered to be a cryptococcal lesion. Elevated levels of lactate and lipids with a relative decrease in the creatine and NAA peak compared to the contralateral normal MR spectroscopy of the right caudate nucleus were noted consistent with necrotic inflammatory process.

Novel therapies for increasing CD4 counts have been studied. Recombinant IL-2 therapy in addition to antifungal agents along with surgical clearance of infection from CNS in ICL patient with Cryptococcus meningitis with subsequent clinical improvement and CD4 increase has been reported. IFN-γ has been shown to be therapeutic to an individual with ICL and Cryptococcus meningitis refractory to antifungals. Animal and in-vitro studies have indicated IL-7 as a promising therapy, and recruitment is underway for clinical trials.
REFERENCES


Dr. Gupta is a third year Radiology resident at Tulane University Health Sciences Center in New Orleans, Louisiana; Dr. Palacios is Section Chief of Neuroradiology and Clinical Professor of Otorhinolaryngology at Tulane University Health Sciences Center in New Orleans, Louisiana; Dr. Neitzschman, now deceased, a professor of Radiology and the Chairman of the Department of Radiology at Tulane University Health Sciences Center in New Orleans, Louisiana.