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by KYLE SANDIFORD, MD CANDIDATE, CLASS OF 2021
LOGAN RUSH, MD, RESIDENT, UAMS DEPT OF DERMATOLOGY

Kevin St. Clair, MD

A 20-year-old college student presents with a widespread, intensely pruritic rash which has progressively worsened over the past two months. It is located diffusely on her body, but is most prominent in her axillae, areolae, waist, and interdigital web spaces. The primary eruption appears to be small, 2-3mm excoriated papules. Using a #15 scalpel blade and mineral oil, scrapings were taken of a few of the papules of the interdigital web spaces and examined with light microscopy (see Figure 1).

What is the next most appropriate step?

A) Topical triamcinolone ointment twice daily x 10 days

B) Praziquantel 20 mg/kg PO three times daily x1 day only

C) Permethrin cream 5% applied from the neck down, and repeated in 7 days

D) Punch biopsy of an intact papule, as the scraping was not diagnostic

E) Examination of the seams of clothing for live lice (*Pedicululus humanis corporis*) or nits (eggs)

Answer: C

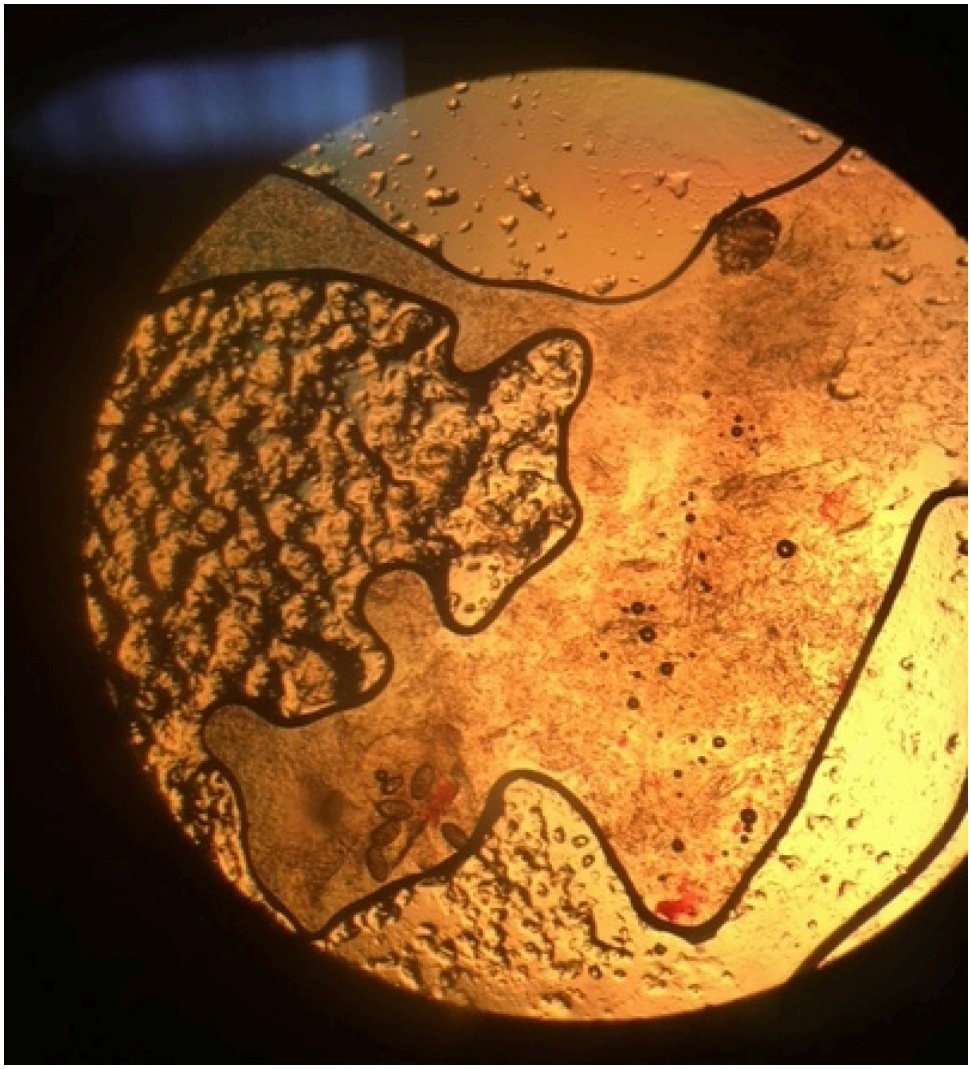

Figure 1.

The photomicrograph above demonstrates the human-specific mite *Sarcoptes scabiei hominis* (dark oval structure upper right of photo). Scabies can have variable clinical presentations, but often presents as pruritic excoriated papules most prominent in the interdigital spaces, flexural creases, areola of women, glans penis, and volar wrists. While observation of burrows (thread-like linear elevations of a few mm length that represent the intraepidermal tunnel resulting from the burrowing of female mites) is highly suggestive of an infestation, definitive diagnosis requires direct observation of mites, eggs, or scybala (feces) on a prepared slide. When a burrow is located on the skin, a drop of mineral oil is placed over the area, followed by a superficial longitudinal scraping motion utilizing a surgical blade. Mite eggs are also observed in the photomicrograph above (small oval structures bottom left).

Therapy should be given simultaneously to household and sexual contacts of the infested patient, and clothing and bedding used in the previous several days should be washed in hot water or sealed in a plastic bag for 3 days. Scabies mites generally cannot survive for more than 3 days off of a human host. Currently, topical permethrin 5% cream (repeated in 7 days) is the treatment of choice; crotamiton and precipitated sulfur in petrolatum are alternative topical agents. Oral ivermectin may also be prescribed. It is important to inform patients that the pruritus may persist for several weeks after scabicidal treatment. •

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by SANDRA MARCHESE JOHNSON, MD, FAAD

Reaching Your Destination in Medicine and in Life

Where the Wind Leads: A Refugee Family's Miraculous Story of Loss, Rescue, and Redemption," by Vinh Chung and Tim Downs, is a skintastic book. Mrs. Nikki Adams, my daughter Anna's AP Literature teacher in Greenwood, discussed this book at student orientation. I encourage you all to read it.

Vinh Chung is a refugee from Vietnam who ends up growing up in Fort Smith, Ark., and becoming a dermatologic surgeon. He is currently practicing medicine in Colorado – our loss, since he is not here in Fort Smith. He has written this book and has come back to Arkansas to share his story and encourage others to pay it forward. I messaged him to thank him for sharing his inspiring story. He replied, "We have all been placed on this earth to make it better." This world would be a much better place if we all lived in a way to try to make our earth better. This book is great. It reminds us how strong the human will and spirit is – particularly that of parents, since we will do almost anything for our children.

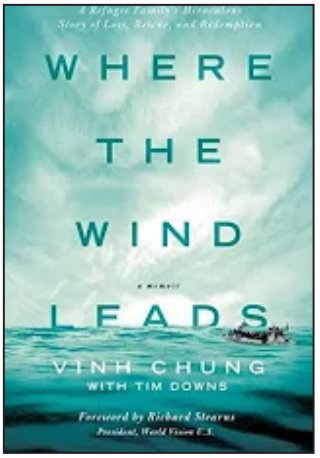
There is a phrase that comes to my mind when thinking about this book: "Change how you see and see how you change." In one section of the book, Dr. Chung discusses so eloquently the difference between a refugee and an immigrant – a contrast that really impacted me. He explains that he and his family are refugees that fled their home out of desperation and with survival instincts to escape their current unsustainable situation. He compares his experience as a refugee with that of an immigrant. An immigrant seeks a new country/place/location with the hope for a better life and more opportunity.

In medicine, especially in dermatology, we are forced to use our knowledge and experience to make critical decisions in a split second. I realize that these skills are useful in medicine, but they may actually be detrimental when it comes to living life. I must admit that I'm usually uneducated or undereducated when it comes to the issues I'm bombarded with through various media channels. Almost every day, I hear about the "immigrant crisis" or "refugees overtaking our country." I'm not sure if all this media bombardment has numbed me to the situation, or if my lack of education prohibits me from processing it appropriately. I do know that "Where the Wind Leads" has changed how I see. I hope I see how I change.

This book resonated with me for many reasons. My mom immigrated from Italy when she was six years old. Because my grandfather did not have all his "papers" in order, they were not allowed to board the Andrea Doria ship and were forced to wait for the next boat. This was fortunate for them because, sadly, the Andrea Doria sunk on that voyage in the Atlantic Ocean. At least 46 people died. When they finally arrived in the promised land of the United States, they lived with a distant family member and her parents found the only work they could find.

They worked tirelessly. As a result, my mom is one of the strongest people I know. She was uprooted to a new country, and no one in her family spoke the language. She started school the week after she came to the U.S. Each day, she learned some English and came home to teach her family. She graduated high school and joined the work force. It was there, when my mom was a shy, 19-year-old girl working in a department store (with her mother who barely spoke English) that my dad approached her and followed her home. When he sought out my mom as a potential date, he was a veteran who recently returned home after hitting a land mine while in Vietnam and then spending six months in a coma and recovering from a femur fracture.

Fortunately for me, my mom and dad dated, eventually married, and had children. Like Vinh's parents, they encouraged their children to study hard and get an education. They encouraged us the best way they knew how to strive for more than they had. They worked hard to provide the best life they could for their children. I'm thankful for the life they have given me and the love they showed me by example.



They repeatedly (as a child and even now as an adult) teach me that my life is a gift from God and that what I do with that life is my gift back to God. They discuss that life is a precious gift and any gift can be taken away at any time – on a ship, on the battlefield, or even in your bed while you are sleeping. Live each day like it is your last. Give your best every day. My dad gave up his dream job of working in the family business of Marchese Construction to take a more stable and higher-paying job on the assembly line of the General Motors plant in Lordstown, Ohio. My parents not only told my sister and me every day that they loved us, they also showed us by example. They worked hard to provide the best they could for us. That is what parents do. We are only more blessed because of the sacrifices our parents made to give us a better life.

I'm thankful for my life. I'm more thankful after reading "Where the Wind Leads." I encourage you to read this book. I ask that you share any inspiring books you read with me. After all, as Dr. Chung states, "Do not believe that you will reach your destination without leaving the shore." Stay skintastic.

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Intramural Pancreatic Pseudocyst Presenting as Gastric Outlet Obstruction Concerning for Gastric Malignancy: Piecing the Puzzle

Gastric outlet obstruction (GOO) is a clinical syndrome comprising epigastric pain and post-prandial vomiting, often due to mechanical obstruction.[1,2] Compression by intramural pancreatic pseudocysts (PP) resulting in GOO is a well-defined phenomenon. We present the first reported case of GOO secondary to pancreatic fistula leading to an intramural fluid collection of the pylorus.

A 54-year-old man with recent cholecystectomy presented with non-bilious emesis lasting four days. Patient endorsed outside hospital admission for similar complaints four months ago, but experienced spontaneous symptom resolution at that time. He had hypoactive bowel sounds but otherwise non-tender, non-distended abdomen. Routine lab work was unremarkable. Computed tomography (CT) without contrast described pyloric heterogeneity and gastric distension, and a possibility of gastric malignancy causing GOO. EGD revealed ballooning around the pyloric opening, raising a suspicion for circumferential pyloric channel tumor (Fig 1). The scope could not be advanced further. Endoscopic ultrasound (EUS) demonstrated a hypoechoic pyloric lesion confined to the deep mucosa (Fig 2). Fine needle aspiration (FNA) yielded dark fluid, the analysis of which showed high amylase (>75,000 U/L). There was one enlarged peri-gastric lymph node, FNA of which was negative for malignancy. Repeat CT with contrast disclosed a 2.4x4.5x5.7cm fluid collection around the pylorus with communication to the pancreatic duct (PD) (Fig 3). Fluid collection was drained endoscopically with subsequent placement of PD stent. Patient later disclosed having a remote episode of pancreatitis and prior surgical pseudocyst drainage, which confirmed our clinical suspicion of pancreatic fistula.

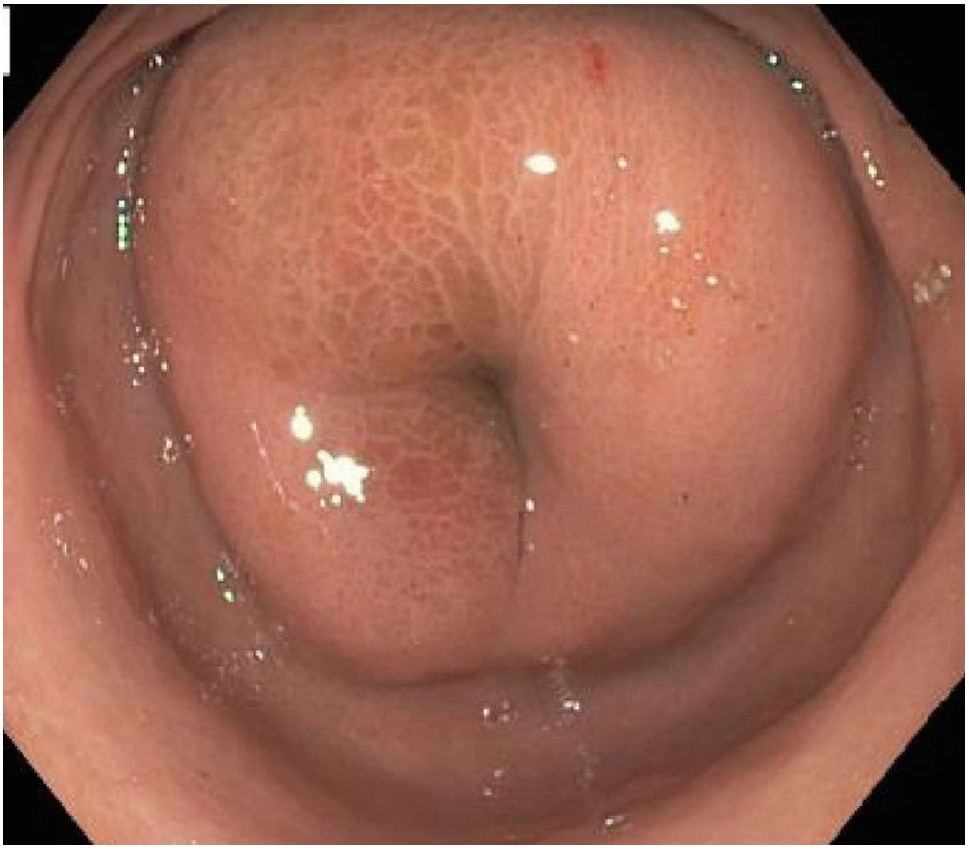
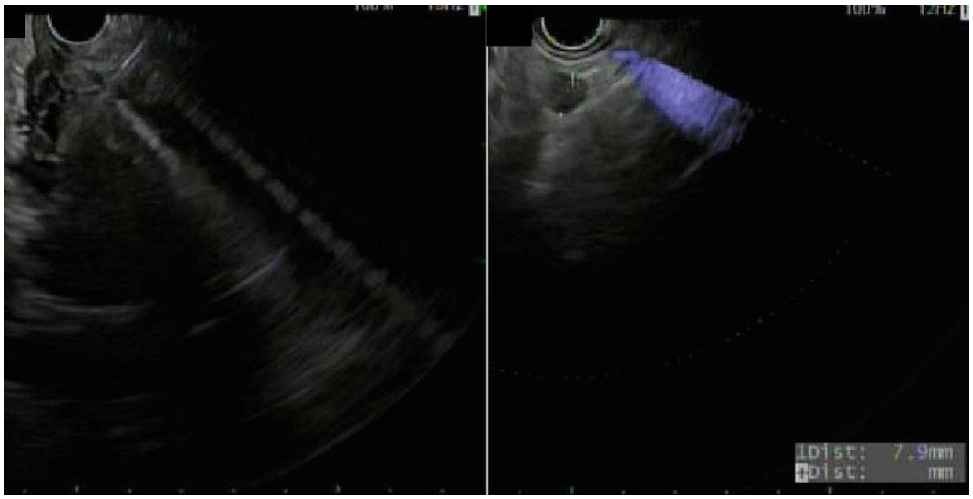


Figure 1

Most PPs resolve spontaneously and uneventfully.[1,3] Rarely, PP may have communication with PD, in which case may arise, a rare complication of fistula formation to other viscera.[1,3] Pathogenesis of PP is believed to be due to disruption of the main PD or peripheral ductules causing leakage and activation of pancreatic enzymes, which further explains the formation of the fistula.[1,3] Symptomatic fistulae present as pain, fever, septicemia, and compression of neighboring structures.[1,2] Endoscopic drainage via cystgastrostomy or cystoduodenostomy is the preferred approach followed by placement of PD stent to allow further drainage and fistula healing.[3] Performed independently, both drainages are effective, safe, and well-coded and the expertise on these procedures is widespread.[3] Surgical drainage is reserved for recurrence or for endoscopic failures.[1,3]

Figure 2



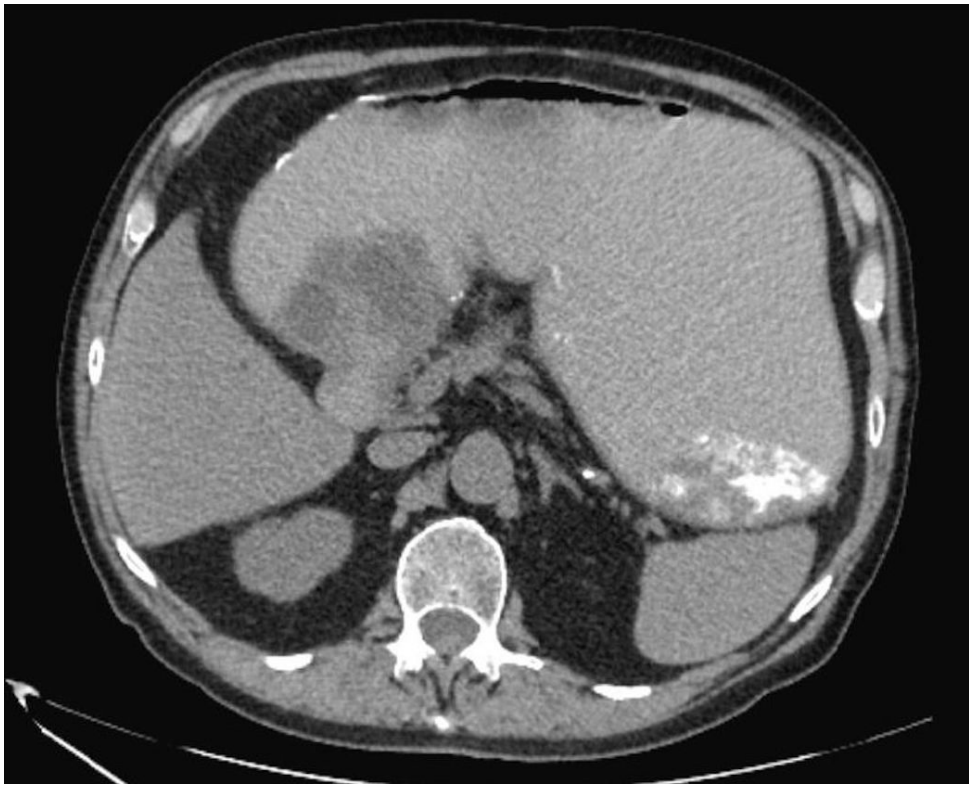


Figure 3

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A CLOSER LOOK AT QUALITY

Spina Bifida: Neuropsychological and Social Implications in Adulthood

LAURA HOBART-PORTER, DO, FAAPMR

Spina bifida (SB) affects thousands of children each year. Due to advancements in urologic and neurosurgical management, there are now more adults alive than children with this historically "pediatric" condition. This has created challenges for adult patients in accessing care with well-informed providers.

The Spina Bifida Association recently published a comprehensive guideline: Care of People with Spina Bifida, spanning birth through adulthood.[1]

In last month's *A Closer Look at Quality* article, I discussed the management of children with SB. This article focuses on neuropsychological, transitional and adult issues.

Individuals with myelomeningocele, a type of SB, tend to have associated Chiari II malformation, hydrocephalus and other congenital brain malformations that can contribute to abnormal neurocognitive functioning. If a shunt is present or has had multiple revisions, it can negatively impact cognitive function. Most patients have some impairment of executive function, namely self-regulation, organization and motivation. Many patients meet criteria for Attention Deficit Disorder, Predominantly Inattentive Type, but do not respond as well to stimulant medications as their typical peers.[2]

Academically, task-switching, mathematics and visual-spatial reasoning tend to be more challenging.[3] Neuropsychological testing can help guide vocational planning and determine if an individualized education plan and 504 accommodations are needed. Vocabulary and grammar are usually relative strengths, but as individuals reach adolescence, social pragmatics becomes a deficit. Pragmatics relate to the use of language in context and can be learned with practice and help from speech therapists or special education professionals.

Neuropsychological deficits can influence relationships, particularly as social conduct becomes more important developmentally.[2] The combination of pragmatics, executive function and attention deficit makes maintaining relationships exceptionally difficult. When we consider the physical impairments and time constraints (therapist and doctor visits, incontinence management breaks), the importance of providing social development opportunities becomes clear.

Individuals with SB should have exposure to activities that allow interaction with typical peers and those who can identify with similar struggles. There are adapted sports and activities available to facilitate interaction. Spina Bifida Camp is especially beneficial for children, encouraging autonomy, self-management and peer relationships. These camps are offered in most states including Arkansas and should include medical staff.[1]

While children with SB often have access to a team of specialists, this is not generally the case for adults. Adults tend to coordinate their own care and independently manage medications, equipment and medical paperwork. These are complex tasks when we consider the typical patient's neuropsychological profile and executive function deficits. If cognitive impairment is severe, families should consider guardianship before their child

turns 18. A limited power of attorney may help for patients with mild to moderate impairments. With either option, get updated neuropsychological testing and speak with legal counsel.

Planning for adult transition should begin early. Encourage young children to care for themselves within their ability, such as picking up toys when young or managing bladder catheterizations as they get older. These small steps have significant implications later in life. Functional independence with bowel and bladder continence is associated with higher income potential and quality of life in adulthood.[1] Include children in treatment plan discussions and encourage participation. If available, patients and family should participate in a formal transition clinic, focusing on health literacy and SB management, starting in the early teen years. Neuropsychological testing will inform the level to which individuals can realistically manage their own care. Testing is available through the Spinal Cord Disorders Program at Arkansas Children's Hospital.

Currently, about 85% of SB patients survive into adulthood.[4] Individuals with higher lesions (above L2) and hydrocephalus are more dependent on help from others for self-care, mobility and bowel/bladder management. Most adolescents trail their typically developing peers by about two to five years in terms of psychosocial development. However, by age 30, approximately one-third will live independently, one-third will require some assistance and one-third will routinely require assistance. A large percentage (43-77%) live with their parents.[5]

While more than half will have a romantic relationship, sexual function may be impaired in adults with SB. Men and women may have altered genital sensation but generally report higher levels of satisfaction with sex than typical peers.[7] Unfortunately, SB patients are vulnerable to sexual abuse, reinforcing the need for developmentally appropriate sexual education.[8]

Most women with SB can become pregnant and carry a child to term.[9] Women at risk for carrying a child with SB should take 4 mg. of folic acid daily and follow with a high-risk obstetrician throughout pregnancy. Pregnant women are more at risk of skin breakdown, elevated intracranial pressure and urinary tract infections. These issues can be life threatening for mother and baby if untreated.

Males with SB may have low sperm health related to abnormal innervation to the testes. If they want biological children, they should consult with a urologist capable of sperm harvesting and storage. Males may require medication or devices to sustain erection.[10]

Adults remain surgically complex, but with different problems than encountered in childhood. Rates of shunt malfunction in adults are lower than in children.[11] Orthopaedic issues such as scoliosis or foot deformity usually have been addressed by early adulthood but may require ongoing management. Knee and hip problems may become more pronounced with age.[12]

Medical concerns shift as children become adults. Skin is less resilient in adults and may be more vulnerable to injury.[13] Sleep apnea remains a consideration and may require respiratory intervention.[14] Risk of cardiac and renal impairment, obesity and diabetes increase with age.[15] Bone density declines with age and may result in fractures if untreated.[16] Physical medicine and rehabilitation specialists often follow adults, managing equipment and therapy needs and assisting with referrals to other specialists. ▲

Dr. Hobart-Porter is medical director, Spinal Cord Disorders Program and Concussion Clinic, UAMS and Arkansas Children's Hospital.

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by SHIFANG WANG, MD; DIANA ABRAHAM, MD; SAI PRASAD DESIKAN, MD; JAY JEFFREY, MD; CHARLES MCCLAIN,III, MD; RAMAN DESIKAN, MD

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Delayed Acute Pancreatitis Induced by Nilotinib in a Patient With Chronic Myeloid Leukemia Attaining Complete Molecular Response

Abstract

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by Philadelphia chromosome t (9:22) (q34; q11) and driven by resultant fusion product, (BCR-ABL1) a tyrosine kinase. Introduction of imatinib, a selective tyrosine kinase inhibitor of BCR-ABL1, resulted in dramatic improvement in response and survival.[1,2] Nilotinib, a second-generation tyrosine kinase inhibitor that is more potent and specific for BCR-ABL, is increasingly employed as front-line therapy and associated with increased and rapid response.[5,6] We would like to report our observation of delayed onset acute pancreatitis in a patient attaining complete molecular response (MR4.5)

Case Report

A 78-year-old Caucasian female was started on nilotinib as front-line therapy in 2013. She tolerated nilotinib therapy other than asymptomatic elevations of lipase and amylase, to a peak of 354 and 82 respectively, which subsided despite continuation of therapy without dose modification. Within two years of starting nilotinib, the patient achieved complete molecular remission of her CML. She continued nilotinib maintenance therapy for the next two years with regular surveillance showing continued response (MR 4.5).

After four years of nilotinib therapy, the patient presented to the emergency department with a seven-day history of abdominal pain in her right upper quadrant and epigastric area, which had acutely worsened over previous three to four days. On evaluation, she had tenderness to palpation in the epigastric region without guarding or rebound tenderness. Vitals at presentation showed a temperature of 97.4 F, heart rate of 80 bpm, blood pressure of 131/69, respiratory rate of 18/min, and oxygen saturation of 95% on room air. Chemistries were significant for an amylase elevated at 154 U/L, lipase elevated at 1775 U/L, and a bilirubin at 1.4 mg/dl. Serum triglyceride at presentation was 149mg/dl. CT scan showed stranding of the pancreatic head, suggestive of pancreatitis, no changes were noted in the common bile duct, and gallbladder was absent (Figure 1). MRCP performed did not reveal abnormalities in biliary drainage including intrahepatic, extra hepatic, and common bile duct. The patient also denied alcohol and recreational drug use. She did not report any abdominal trauma. Review of drugs revealed nilotinib as probable cause of drug-induced pancreatitis. Nilotinib was discontinued. She improved significantly with supportive care; on discharge after four days of hospitalization, lipase level was down to 353U/L. Due to complete molecular response to nilotinib (MR4.5), she was observed closely without any further therapy. Molecular remission has persisted for over a year on close monitoring.

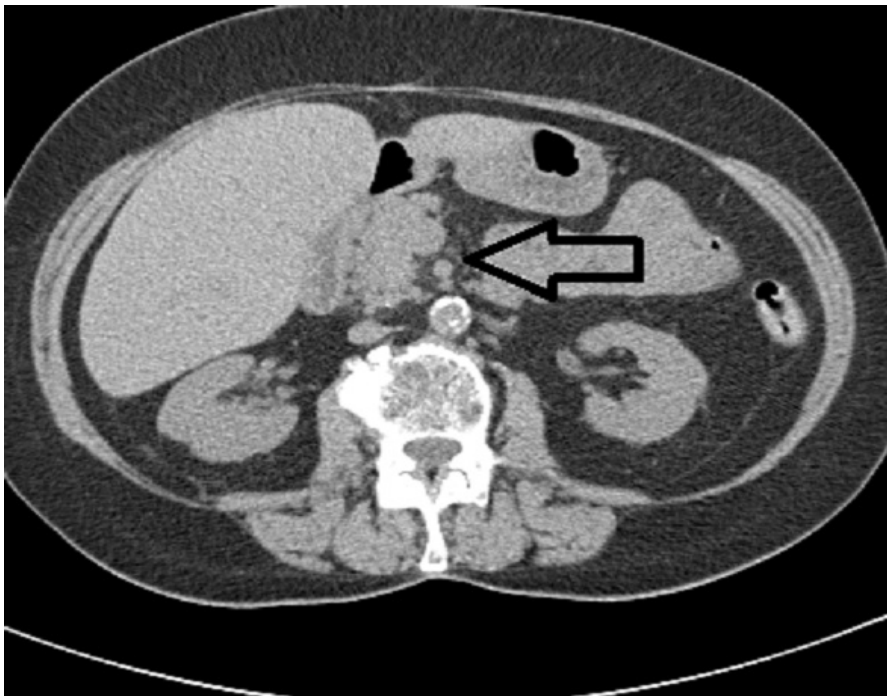

Figure 1: Black arrow indicates peripancreatic stranding consistent with pancreatitis.

Discussion

Chronic Myelogenous Leukemia (CML) is a myeloproliferative disorder characterized by the overproduction of myeloid cells from unrestrained expansion of myeloid pluripotent stem cells. The characteristic abnormality results from reciprocal translocation of chromosomes 9 and 22, resulting in der9q+ and 22q-, called the Philadelphia chromosome. The resultant BCR-ABL1 fusion protein with constitutive tyrosine kinase activity is necessary and sufficient for pathogenesis of chronic phase CML.[1] Introduction of imatinib, a tyrosine kinase inhibitor, revolutionized therapy of CML. Compared with interferon and Ara C, Imatinib resulted in improved major cytogenetic response, complete cytogenetic response and improved progression-free survival. Improvement in overall survival was not significant because of crossover. However, imatinib improved overall survival compared to historic trials with interferon.[1,2] With significant improvement, response is determined by mo-

Table 1

Classification	Detectable disease	BCR-ABL1 transcript to ABL1 transcript ratio	Log reduction	Optimal duration of therapy to reach classification
MR2	≤ 1%	≤ 1:100	2	6 months
MR3	≤ .1%	≤ 1:1000	3	12 months
MR 4	≤ .01%	≤ 1:10000	4	Anytime
MR 4.5	≤ .0032%	≤ 1:32000	4.5	Anytime

lecular testing with standardized real quantitative polymerase chain reaction (RQ-PCR); sensitivity is high for low-level residual disease (10-4 to 10-5). Molecular response is assessed in accordance with international scale (IS) as ratio of BCR-ABL1 transcripts to ABL1 transcripts or other internationally recognized control transcripts and reported as BCR-ABL1% on a log scale[3] (Table 1). Long-term follow-up has been published for imatinib cohort (median – 10.9 years), which confirms excellent outcome. Ten-year overall survival was 83.3%; more importantly, CML specific survival was better in patients attaining major molecular response at 12 and 18 months (MR3). Despite these impressive results, about one-third of patients need improved outcomes. 18 percent of patients did not achieve complete cytogenetic response; 19 percent of patients who attain complete cytogenetic response lose their response, and 4 to 8% of patients are intolerant to imatinib therapy. Niltoinib, when compared with imatinib, resulted in earlier and higher rates of major molecular response and lower risk of progression to accelerated phase or blast. Long-term follow-up confirmed improved response (MR4.5) 54% and 52% in two nilotinib arms compared to 31% with imatinib. Long-term toxicities were not significantly different, making this a valuable option.5-7 Our patient achieved and maintained complete molecular response (MR4.5).

Our patient tolerated nilotinib therapy without significant toxicities. Asymptomatic and transient elevations of pancreatic enzymes that were noted resolved without dose reduction or discontinuation of nilotinib. Asymptomatic elevations in pancreatic enzymes have been observed in approximately one-third of patients, including grade 3-4 in 18% of patients, which is usually not associated with acute pancreatitis. Median time from start of nilotinib to elevation of pancreatic enzymes was three months. Pancreatic enzyme elevation was isolated or transient in most patients. Occasional drug interruption was necessary.[8] The underlying reason is unclear; suggested mechanisms include inhibition of non-receptor tyrosine kinase C-abl, calcium release from intracellular stores, and accumulation of fatty acids in the acinar cell.[9]

Acute pancreatitis is much less common, around 1%, and occurs relatively early after start of nilotinib. Acute pancreatitis has been observed after initiation of other tyrosine kinase inhibitors in therapy of CML and other malignancies. Delayed occurrence of pancreatitis has not been reported thus far.[8-11] Acute abdominal symptoms, magnitude of pancreatic enzyme elevation, and CT imaging was consistent with the diagnosis of acute pancreatitis on Atlanta criteria and graded as mild, based on revised Atlanta criteria.[12] The patient was diagnosed with acute drug-induced pancreatitis by exclusion of other causes. Drugs account for 2% of cases, usually mild to moderate, and resolve with the discontinuation of drugs.

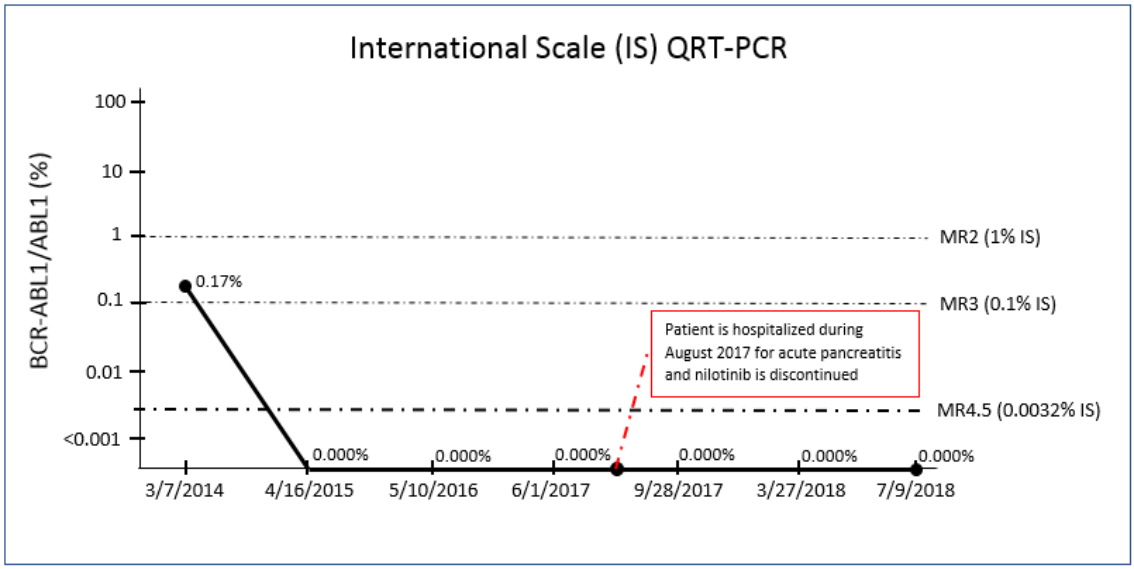

Figure 2: patient's timeline for QRT-PCR showing treatment response and monitoring after discontinuing nilotinib.

Drugs other than nilotinib implicated in acute pancreatitis on her medication list included Lisinopril, pravastatin, metformin and furosemide.[13] Nilotinib was discontinued on day two of hospitalization, and patient showed prompt reduction in enzyme elevation and clinical symptoms. She has since had no recurrence of pancreatitis, despite continuation of all other medications.

Nilotinib was discontinued, and the patient was not started on alternate tyrosine kinase inhibitor; the recurrence of pancreatitis on alternate agent has not been well-studied. Discontinuation of nilotinib has been well-studied in Phase 2 trial in patients with sustained deep molecular response (MR4.5). Molecular response was sustained for more than 12 months in more than 50% of the patients. Majority of patients (>90%) reinitiated on nilotinib due to loss of major molecular response (MR3.0) regained major molecular response.[14,15] On close monitoring, she continues to show deep molecular response a year from discontinuation of nilotinib (Fig. 2).

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I am a member of the AMS because they provide support for physicians in the state and serve as a voice for physicians. As a Board of Trustees member, I am able to meet other physician leaders from across the state and build relationships.

I have enjoyed serving in the Society's Doctor of the Day program at the state legislature and have been able to observe the legislative process to see how bills that impact our practice are decided. I have been able to meet my local senator and state representatives and have been more involved in communicating with them to voice my support or opposition to various bills that impact medical practice and care of patients in the state.

Ngozi Ada Wilkins, MD, MPH
Nashville, AR
AMS District 6 Trustee

I decided to become a member of the AMS several years ago because I felt it was important to have a voice in the promotion of physicians' interests. I strongly believe that physicians in Arkansas are very dedicated and that we need to stay organized and unified to make Arkansas the best place to practice - it will only help to recruit more physicians to the state.

Shane Smith, MD
Jonesboro, AR
AMS District 1 Trustee

SCIENTIFIC ARTICLE

by KAPIL ARYA MBBS, MD[1]; AMIT AGARWAL, MD[2]; VIKKI STEFANS, MD[3]; ARAVINDHAN VEERAPANDIYAN, MD[1]

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Spinal Muscular Atrophy: the Changing Landscape of Diagnosis and Management in Arkansas and Beyond

Abstract

Spinal muscular atrophy (SMA) is a neurodegenerative, autosomal recessive disorder usually due to biallelic deletions or, in rare cases, inactivating mutations of exon 7 of the SMN1 gene. Clinical classification is based on the highest motor milestone achieved. Intrathecal nusinersen treatment, the first disease modifying therapy approved by the U.S. Food and Drug Administration, produces improvements in motor function for patients with SMA. Also, single-dose SMN gene replacement therapy shows very promising results and awaits FDA approval. Research indicates that early treatment leads to the greatest benefit, emphasizing the need for newborn screening for SMA.

Introduction

Spinal muscular atrophy (SMA) is an autosomal, recessive severe motor neuron disease and the leading genetic cause of infant mortality, affecting approximately 1 in 10,000 babies. About 1 in every 50 Americans is a genetic carrier for SMA.[1] Patients are roughly categorized into one of four types of SMA clinically, based on age of symptom onset and the highest physical milestone achieved. Type I SMA has symptom onset before the age of six months, and patients generally do not attain the ability to sit independently. Typical clinical manifestations include neonatal hypotonia, proximal weakness, tongue fasciculations, and areflexia progressing to respiratory and bulbar weakness. There may be reduced fetal movement in utero. Children with type II SMA may have slightly later onset of symptoms, often between six and 18 months of age; they achieve independent sitting, but are typically unable to walk. Children with type III SMA become symptomatic after 18 months of age, may have preserved reflexes that gradually diminish over time, can typically stand and walk, and have a wide spectrum of motor functional impairment. Type IV is the mildest form of SMA. It is adult onset with very slow progression. There is also a form of later adult onset autosomal dominant disease due to mutation of a different gene that is outside the scope of this discussion. Cognition is preserved in all types. Prognosis is varied based on the clinical severity across the four types and within each type.[2] Failure to achieve motor developmental milestones or, in less severely affected patients, a gradual loss of acquired motor milestones, is due to hypotonia plus weakness. Weakness is typically more profound in the lower than the upper extremities, where antigravity function may be preserved. Fine motor effects and tremor, if present, are relatively mild.

Genetics

SMA is caused by homozygous deletion or mutation of survival motor neuron 1 (SMN1) gene at chromosome 5q. Genetic diagnosis is made by deletion/duplication analysis and/or gene sequencing from blood samples. SMN1 produces survival motor neuron (SMN) protein, which is present in the cell body, axons, and dendrites of motor neurons. Absent or insufficient levels of SMN protein leads to the selective death of spinal motor neurons, possibly mediated by dysfunction of small ribonuclear proteins that affect splicing of other essential genes. A second and almost identical gene, survival motor neuron 2 (SMN2), is present in most human genomes and makes low levels of SMN protein. During SMN2 splicing, a small segment of required RNA, exon 7, is excluded from the final mRNA transcript; this results in the production of mostly truncated and rapidly degraded SMN protein, with only 10-15% functional SMN protein. Thus, the greater the number of SMN2 copies, the milder the SMA phenotype. Most children with type I SMA have only one or two SMN2 copies, most with type II have three copies, and with type III or IV there are three to four copies or more. Some infants with one copy are very severely affected and unable to breathe independently at birth. It is thought that with no copies, the condition is lethal in utero, accounting for the discrepancy between carrier rate and birth rate. SMN2 production does not directly make up for the loss of SMN protein production from SMN1, but the SMN protein production is increased proportional to the SMN2 copy number. Therefore, the number of SMN2 copies is inversely related to symptom severity and clinical subtype. However, considerable variation in clinical phenotypes can occur both between patients with the same number of SMN2 copies. Research on discordant families has led to the identification of several genetic modifiers of SMA, including plastin-3 and neurocalcin delta. It is likely, therefore, that further genetic and other disease-modifying factors are still to be discovered.[1,2,3]

Management

Historically, the management of SMA focused on symptomatic and supportive treatment, with an emphasis on supporting ventilation. There is progressive respiratory failure. Ineffective cough is a result of respiratory muscle weakness and contributes to repeated respiratory infections. The goal of pulmonary management is to normalize gas exchange by decreasing atelectasis; this is achieved by airway secretion mobilization and clearance, assisted coughing, and respiratory support via invasive or non-invasive ventilation. Supplemental oxygen is not the first line of treat-

ment. Neuromuscular scoliosis is often seen and may need surgical correction. Intensive physical and occupational therapy is important to maintain range of motion and decrease disability. Often orthotics and mobility assistance, for example with a power or ultralight manual wheelchair, are also needed. Patients with severely abnormal swallowing may need feeding through a gastrostomy tube. Osteopenia also needs management with supplements or medication like alendronate. Airway obstruction in sleep may need to be managed with a bilevel positive airway pressure (BiPAP) device. However, even with intensive management, until very recently, the natural history of the disease was that of gradual but inevitable motor decline and usually early death.2,4,5

New Disease-Modifying Therapies

Happily, the bleak prognosis and natural history of this disease may change with the availability of disease-modifying therapies aiming to improve motor function. Nusinersen is the first and only such therapy currently approved by the U.S. Food and Drug Administration. Considering the pathophysiology of the disease, boosting SMN protein production from SMN2 by promoting exon 7 inclusion is an obvious target. This is achieved by nusinersen, a synthetic antisense oligonucleotide (ASO). ASOs are lab-designed, short ribonucleic acid (RNA) pieces that are a mirror-image of the natural RNA that they bind to. Nusinersen masks portions of the SMN2 messenger RNA that inhibit the exclusion of exon 7. This allows for the inclusion of exon 7 into the SMN2 final mRNA transcript, resulting in production of more full-length normal SMN protein. Nusinersen improves motor function in all SMA types and prevents disease onset/progression in pre-symptomatic patients. ASOs do not cross an intact blood–brain barrier, so the drug is injected intrathecally with the recommended treatment regimen of four loading doses: the first three doses at 14 days interval, fourth dose 30 days after the third dose, and maintenance dosing every four months thereafter. Besides the obvious involved process of drug administration and attendant discomfort to the patient, side effects are relatively minimal. The drug is eliminated by the body unchanged in the urine. Prothrombin time, platelet count, and urine proteins need to be monitored prior to each nusinersen injection to screen for development of clotting problems or kidney injury as mild thrombocytopenia and elevated urine protein were noted in minority of patients treated in the clinical trials. Although this medicine is not curative, results are encouraging with about 50% of the treated patients showing improvements in the motor evaluation measures.[2,6]

A gene therapy product for SMA awaits FDA approval. The best approach for treatment, considering the genetics of SMA, would be to replace the absent SMN1 gene. The relevant genetic material is delivered via a viral vector, Adeno-Associated Virus 9 (AAV9). A single-dose intravenous infusion of AAV9 vector containing DNA coding for SMN protein resulted in longer survival, superior achievement of motor milestones, and better motor function in patients with type 1 SMA than in historical cohorts.[7] It is proposed that infants will receive a one-time intravenous dose, and older individuals a one-time intrathecal dose of this product. Trial results are very encouraging. Other potential therapies are undergoing trials. Oral medication to boost SMN production from SMN2 is being tested. SRK-015, a highly specific inhibitor of myostatin activation, is being evaluated for efficacy. Research is underway to identify potential modifiers in SMA, including the gene plastin, which has been reported to modify SMA symptoms in female patients, but not male patients. Other cellular pathways such as the mTOR, U12 splicing/stasimon, or the p38□MAPK pathway that are altered in SMA and may contribute to how the disease develops, are also being studied.[2,3,6]

Conclusion

The recent advancements in the treatment for SMA necessitates the care in a multidisciplinary

setting with health care providers with expertise in managing these patients. The 2007 consensus guidelines and the update published as Part 1 and Part 2 in 2018 established the need for a multidisciplinary approach to SMA care. Such comprehensive care for patients with SMA may best be achieved at a tertiary care center.[2,6]

Ongoing research has shown that beginning therapy as early as possible in children with SMA is critical. Studies indicate therapy is most effective when it can begin in the first few months of life before significant motor neuron loss occurs as well as in pre-symptomatic infants. This research reinforces the need for newborn screening, which would eliminate long and costly diagnostic delays and allow pre-symptomatic therapy. The CureSMA advocacy group lobbied the U.S. Congress to include SMA in the Recommended Uniformed Screening Panel for newborn screening. Several U.S. states initiated pilot programs in 2018, and the testing has been shown to be highly specific and sensitive. It is gratifying that in Arkansas, Governor Asa Hutchinson has signed a bill (HB 1074) into law that requires testing for SMA be added to the state's newborn screening panel. This will allow for genetic diagnosis soon after birth, potentially even before onset of any symptoms.[8,9,10]

In conclusion, patients with SMA, a previously incurable and debilitating disease, now have a chance to greatly modify the condition and thereby extend the length and improve the quality of their lives.

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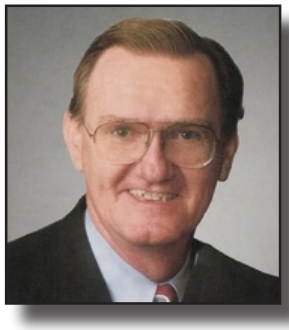
OBITUARY



SALEM - Dr. Michael Neill Moody, 73, of Salem, Arkansas passed away December 15, 2019, in Salem.

Michael was born August 18, 1946, in Batesville, the third of six children of John Jr. and Ruby Faye Moody. An above average student and avid athlete, when he wasn't on the basketball court or ball field, Michael was in the Fulton County Library – so much so that if he was late for supper, his mom would call the librarian for him to come home.

Michael graduated from Salem High School and attended Arkansas College in Batesville on a basketball scholarship. When ball practices interfered with pre-med biology lab, he transferred to Arkansas State University to pursue his dream of attending medical school and becoming a family doctor in his hometown of Salem. And he did just that, graduating from University of Arkansas for Medical Sciences and practicing in Salem for more than 45 years. A board certified family practice doctor until 2013, "Doc Moody" is best known for delivering and taking care of multi-generational families. In addition to practicing medicine, he loved skiing the mountains of Colorado, the Arkansas Razorbacks, and hunting everything that flew. He was known statewide for his "Doves on the Deck" party every year on opening day of dove season, but quail was his favorite bird to hunt. In fact, he was often blamed for the decline in their population in Arkansas.

As a physician, Michael served in a number of leadership roles with the Arkansas Medical Society, the Arkansas Academy of Family Physicians, and their national affiliates. He was Medical Director of the Arkansas Foundation of Medical Care for 20 years and continued as a board member until his illness. But of all his many accomplishments and accolades, his true passion was medicine. His favorite thing to do was take care of his patients, in his clinic as well as in Little Rock. He was known at the State Capitol as the champion for rural medicine, being sought out by legislators and regulators for his expertise. As one of the first four graduates of UAMS's Family Practice Residency, he spent his entire career advocating for patients. One of his proudest successes was the passage of Any Willing Provider legislation, which grants patients the freedom to see the doctor of their choice.

Michael is survived by his wife Barbara of Salem, three children, Scott Moody of Salem, Melissa Moody of Little Rock, and Karla Moody McBride of Kalamazoo, MI; three grandchildren, Brice Allen Langston, Conner Marie McBride, and Maggie Mae McBride; 5 siblings, Sue Lackey (Louie) of Little Rock, Jerry Moody of Salem, Connie Bray (Sonny) of Salem, Johnny Moody (Rhonda) of Salem, and Steve Moody (Nancy) of Dalton; his nurse of 29 years Sheila Cochran, a slew of nieces and nephews, friends, colleagues, and hunting buddies

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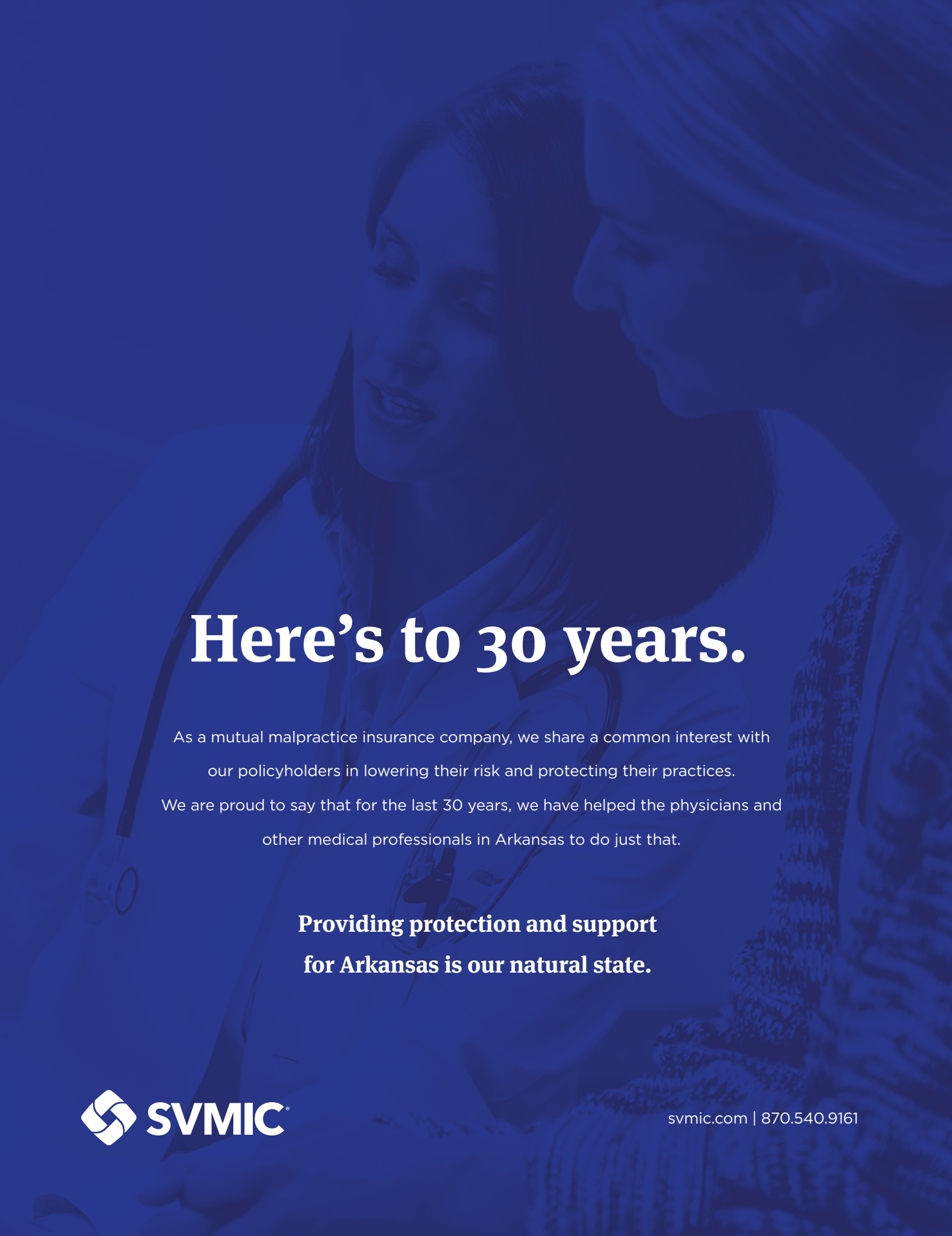
The Arkansas Medical Society will sponsor the Doctor of the Day program for the 2020 fiscal session of the Arkansas legislature.

The session convenes on Wednesday, April 8, 2020, and will continue for 30 days, but it can be extended one time for an additional 15 days by action of the legislature.

Volunteers are needed each Tuesday, Wednesday, and Thursday only. The fiscal session committee schedule varies from the regular session in that, usually, only the Joint Budget Committee meets.

Contact Laura Hawkins at 501-224-8937 or hawkins@arkmed.org if you have questions or would like to sign up. **Space is limited.**



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