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With the wrap-up of the 2013–2014 academic year, we are proud of the strides that Medical Student Research Journal (MSRJ) has made. The journal has grown in the number of issues as well as in the number of articles published per issue. In addition, the breadth of article types and topics has greatly increased. This spring issue includes works from the Royal College of Surgeons in Ireland, University of the East Ramon, University of East Anglia Norwich Medical School, and Michigan State University College of Human Medicine.

The production of regular issues creates the drive for continued submissions which always astounds our editorial team in both number and quality. Because of this, our staff continues to expand each year, making it possible to accommodate the increasing domestic and international submissions and readership. As our annual student elective successfully comes to an end, we have accumulated a fresh group of enthusiastic students ready to take on the junior editor role. The incoming group of junior editors brings new ideas, not only about the annual reviewing and publishing course elective but also for future developments meant to strengthen the journal. The current staff is excited to begin a new year at MSRJ and teach new staff the ropes.

We congratulate all of our graduating fourth year medical students as they move on to incredible residency positions. I will be moving on to Ohio State University for Internal Medicine; Jon Zande, one of our senior editors, will be beginning his Neurology residency at Case Western Reserve University – University Hospitals; and Skyler Johnson, another senior editor, will start his Radiation Oncology residency at Yale University. Jon and Skyler will be greatly missed, but we wish them the best of luck as they embark on the next part of their careers.

I am proud to say that over the past year, the journal has made progress by instituting more education about scientific writing and publishing, greater social media coverage to involve a larger group of people, expanded website resources and information, gained further support from our college, and increased visibility with indexing services, as well as further establishing journal permanence. I have observed MSRJ undergo an incredible amount of change over the past 3 years as a member of the board and over the past year as executive editor. This has been a vast learning experience and will always have a lasting impact on my future in academic medicine. It is saddening to leave the journal and this amazing team, but I know MSRJ will continue to improve and expand. I hope to have left a lasting impression on the journal in its educational aspects to encourage others to expand their thinking, analysis, writing, editing, and publishing skills.

As with the end of each academic year, the leadership at MSRJ changes to bring in new leadership and perspectives to the journal; Jessica Wummel will continue as executive editor for the 2014–2015 year, and Jack Mettler will be promoted to deputy executive editor for the same term. The March editorial-board meeting brought out an amazing set of ideas from new leaders, with a comprehensive set of goals, and strong contributions from the rest of the board. There is no doubt that this new leadership team will continue the excellent publication and education goals that MSRJ has strived for and produced since its inception.

As always, we thank the Michigan State University College of Human Medicine for their ongoing support. This journal would not be possible without the talented and dedicated staff taking time out of their busy schedules to promote MSRJ. Our readers are invited to follow the progress of the MSRJ both on Facebook and Twitter, and on our website at http://www.MSRJ.org. As the journal’s editorial base expands, it is making room for more submissions and providing more education for the aspiring physician–researchers/educators/learners.

Sincerely,

Kevin C. Patterson
Executive Editor – MSRJ 2013–2014
my grandfather passed away the day after Christmas in 2012. He was a brilliant man who practiced medicine for several decades. During that time, he delivered thousands of babies, and even performed the amniocentesis on my mother when I was a fetus. Yet, in his last months, his failing health did not convey this brilliance. Parkinson’s disease and other neurological issues prevented my grandfather from speaking quickly or coherently. This was tough to witness, but it taught me an important lesson: there is much more to a patient than just the information contained in his/her medical file. This concept was the inspiration for my artwork.

For this piece, I drew a portrait of an elderly man, not so different in age and appearance from my own grandfather. On the left, the man’s muscles, bones, and anatomical structures are visible with accompanying labels. On the right, the man is seen from an external view with labels describing some of the unseen personal components of his life.

My intentions for this project are to portray the balance that all physicians must find between
understanding a patient’s medical story, as well as understanding his/her personal story. Neither is complete without the other, and it is the physician’s duty to explore both facets to build relationships with patients and find the best way to treat them. I hope that in my future practice, I will effectively build these relationships by not only administering effective medical care but also by taking the time to learn about patients’ lives, personalities, and values.

Original artwork inspired by “Study of an Older Man” by John Norman Stewart, 2010 and “Musculature of the face with the orbit of the eye” by Nicolas Henri Jacob, 1831.
Future Medical Practice and Genetics

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Significant progress has been made in the rapidly evolving sub-specialty of medical genetics. In this article, breast cancer has been used as an example to highlight recent developments in this field of medicine, with a discussion on the implications this has on medical practice and policy. The potential of medical genetics is staggering but not without its limitations, and we must consider all aspects of use before advancing further. Consequently, students and physicians alike need to have a thorough understanding of all components of clinical genetics in order to be ready for this new era of healthcare.

Keywords: medical student; breast cancer; single nucleotide polymorphisms; genome-wide association studies.

INTRODUCTION

Our understanding of medical genetics has grown rapidly, with major discoveries in the structure and function of DNA since Mendel’s experiments in plant hybridization, published in 1865.1 These discoveries have formed the basis of screening programs and treatments, which were inconceivable earlier. In 1990—the year the Human Genome Project commenced—53 genes were known to cause disease. After less than 25 years of research, we have identified over 2,900 disease-related genes.2 This knowledge has empowered the medical profession with non-invasive diagnostic techniques and sophisticated therapies that now supersede invasive methods. Antenatal diagnosis of Trisomy 21 (Down syndrome) demonstrates this point; multiplexed maternal plasma DNA sequencing has the potential to be a more effective and safer screening tool compared to traditional, invasive, and costly methods such as chorionic villous sampling (CVS) and amniocentesis and may even eliminate up to 98% of invasive diagnostic methods.3

DISCUSSION

Even for medical students planning to pursue careers outside of genetics, it is inevitable that they will encounter variants in their patients’ genetic constitutions that have contributed to the disease phenotypes from which they suffer. The importance of genetics is becoming well-recognized in many conditions with an increasing prevalence, including hypertension and type II diabetes mellitus, which are now known to have a polygenic and multifactorial basis, respectively. Substantial evidence of the interaction of multiple genes with each other and the environment through various mechanisms has furthered understanding of these diseases.

It is essential that medical students acquire the clinical skill of taking a complete family history to determine the risk involved and offer treatments appropriately. Furthermore, familiarization with new techniques involved in genomic analysis when samples are sent for genetic testing will ensure appropriate investigation, selection, and interpretation. Above all, a doctor’s ability to take a thorough family history could be the difference between an affected patient receiving proper screening, treatment, or prophylaxis for early stage disease, identified via testing, and presenting with advanced and potentially incurable disease.

A prime example is cancer, which has historically afflicted families with grief, stress, and uncertainty of their own future. Thankfully, patients with a known family history of specific cancers or gene mutations can now receive genetic counseling from the National Health Service (NHS) in the United Kingdom. Since the completion of the Human Genome Project in 2003, costing $3 billion (£1.81 billion) and taking 13 years,1 the accessibility and affordability of genome sequencing has dramatically improved. Major commercial competition has brought down the cost of whole genome sequencing, with the analysis completed in a matter of days for as little as $6,995 in April 2013.4 Many companies are currently striving to achieve sequencing at a cost of $1,000 by the end of 2014. With the link yet to be made between many genetic abnormalities and viable
treatment options, it could be argued that this test is currently academic in most cases. Consequently, in the foreseeable future, many patients could present with results from privately obtained genome sequencing that potentially require action, possibly in the form of increased surveillance, treatment, or genetic counseling of relatives. Such health-seeking behaviors may increase the workloads of general practitioners and specialists alike, demanding confidence in their own understanding of genetics to effectively communicate a multitude of genetic concepts, particularly regarding genetic susceptibility.

Some clinicians may believe that assessing whether a patient meets the referral criteria for genetic testing is the extent of their application of genetics in practice. This attitude is likely to change significantly. Progress in the diagnosis and treatment of breast cancer can be used to demonstrate how changes in this field of medicine are changing clinical practice. Breast cancer is the most common female malignancy with a lifetime risk of 8–10%, and much research has been done looking into this disease. Moreover, breakthroughs achieved in the genetics of breast cancer can be applied to a wide range of other conditions with a genetic component.

In broad terms, two main groups of genetic susceptibility have been established with regard to breast cancer. Rare, highly penetrant monogenic mutations in fundamental DNA repair genes on the one hand and multiple, relatively common, low penetrance Single Nucleotide Polymorphisms (SNPs), which confer an increased risk to breast cancer, on the other. However, breast cancer has presented epidemiologists and geneticists with a number of difficult questions, especially why no genetic mutations can be attributed to over 70% of cases of breast cancer in which there is a significant familial clustering. Many advances have helped answer this question by providing powerful evidence that has changed how we approach cancer genetics. These findings have implications for the clinical treatment of other diseases and are on course to bring about change with improved outcomes.

Physicians have already recognized their new role in medical practice and now acknowledge the need to appreciate the genetics of disease in order to optimize clinical outcomes. Surveys have found that results from the 21 gene assay, a genetic test that provides a likelihood of recurrence of breast cancer, influence the decisions made regarding adjuvant therapies in breast cancer, with a 19% reduction in the rate of chemotherapy recommendations and a 15% increase in hormonal therapy recommendations.

Through comparison of allele frequencies in candidate genes between breast cancer cases and unaffected controls, genome-wide association studies (GWAS) have been the driving force for vast progress with regard to our knowledge of genetic susceptibility. Conclusions drawn from such studies continue to support the widely accepted notion that breast cancer exhibits a polygenic model of inheritance. Emerging evidence supports the assertion that, in the vast majority of cases, multiple genes are responsible for producing the breast cancer phenotype, involving a large number of low-risk variants with a cumulative effect in determining the overall risk. Many of these mutations are thought to coexist in highly penetrant combinations.

It is interesting to note that monogenic mutations in breast cancer 1 and 2 (BRCA 1 and BRCA 2) have received the majority of the media’s attention despite being responsible for less than 5% of the total cases of breast cancer. BRCA-positive patients are informed that they have up to an 80% risk of developing breast cancer. However, variation is commonly witnessed in these patients in terms of penetrance, receptor status, and natural history. Modifier genes have been offered as an explanation for differences observed in these patients; research to determine the genes with silencing or enhancing effects of other gene mutations that may contribute is ongoing. It has been speculated that modifier genes may also have an effect on the risk factors associated with breast cancer. Risk factors such as mammographic density and age at menarche are being scrutinized through GWAS to establish the SNPs involved in the expression of these phenotypes. Although this research is still in its infancy, it has the potential to take us even closer to accurately determining individualized risk.

Over the past decade, molecular genetics has facilitated the construction of a pathophysiological ‘map’, illustrating the roles and interactions of all the genes known to be involved in fundamental pathways, including the DNA damage response network. Susceptibility genes may operate at any level within this network, from sensing the DNA lesion through to transduction of the damage signal (e.g., ATM) or even effector roles in cell death or repair pathways (e.g., BRCA1/2). Consequently, it is possible to relate each identified mutation to a loss of gene function and thus the associated risk. For example, using existing knowledge of the molecular mechanisms involved in the DNA damage response
network, Bartkova et al.\textsuperscript{10} identified \textit{MRE11} as a new possible candidate gene in BRCA-negative patients that operates through sensing the double stranded break in DNA.

As of June 2012, 25 SNPs had been implicated in the pathogenesis of breast cancer,\textsuperscript{11} with many involved in different stages of a common pathway. However, the clinical consequence of many of these genes is not yet clear, and, as a result, genetic testing for these SNPs as a means of risk stratification is not yet justified. Importantly, these developments may be applicable to sporadic cases, which constitute over 70\% of breast cancer cases.\textsuperscript{6}

We are already at a stage of using individual genomic information to inform treatment decisions. For example, the genetically determined \textit{HER-2} receptor status of the tumor is used to determine whether trastuzumab (Herceptin) should be used in the treatment of breast cancer. Similar drugs (e.g., gefitinib) exist for EGFR receptor--positive lung cancer, demonstrating that this area of medicine is already making an impact in the survival of cancer patients. The fact that somatic mutations are being used to inform treatment decisions demonstrates that this new approach can be applied to the management of all breast cancer cases and transferred to other cancers with known genetic markers.

Genetic risk prediction models have been developed to optimize patient care.\textsuperscript{12} Such models have raised a number of ethical and legal issues that must be considered when implementing genetic testing in clinical practice.\textsuperscript{13} Using risk prediction models arguably enables clinicians to offer testing only to those who are likely to benefit. Equally, it may spare unnecessary investigations and treatment in those unlikely to benefit, thereby abiding by the principles of non-maleficence and beneficence, respectively.\textsuperscript{14} Providing treatment in this way is also likely to be more cost-effective. However, current risk prediction models for breast cancer favor only patients with more extensive knowledge of their family history.\textsuperscript{15} Furthermore, the use of genetic information may create inequalities in the context of employment or health insurance, suggesting that such models may act as vehicles for ‘genetic discrimination’.\textsuperscript{16}

The National Human Genome Research Institute (NHGRI), which is part of the National Institutes of Health in the United States, created the Clinical Sequencing Exploratory Research program in 2010, which focuses on the technical, ethical, psychosocial, and clinical implications of genetic testing.\textsuperscript{17} Research into this sensitive area is ongoing and is required if the true potential of genetic testing is to be realized.

CONCLUSION

Through exploring the vast progress made in breast cancer diagnosis and treatment over a short period of time, the potential for individualized diagnosis and treatment of this disease is obvious. In recent years, the discovery of a large number of relevant SNPs identified through GWAS has enabled risk stratification at a far greater level of detail than achieved with previous methodology. Our knowledge is being translated into techniques that are being integrated into daily practice. Given that parallel progress has been made across a wide array of conditions, it is evident that we as medical students will be entering into a new world of medicine and we owe it to our patients to be prepared for it.

Conflict of interest and funding: The authors have not received any funding or benefits from industry or elsewhere to conduct this study.

REFERENCES

Introduction and Patient Profile: Introduction of deep enteroscopy (capsule endoscopy (CE), balloon-assisted enteroscopy, and spiral enteroscopy) has led to a significant improvement in diagnosis and management of obscure gastrointestinal bleeding (OGIB). Small bowel (SB) lesions are traditionally discovered by CE or double balloon enteroscopy (DBE). Leiomyosarcomas are rare SB tumors and must be diagnosed early to prevent the risk of metastasis and to improve prognosis. A 46-year-old previously healthy woman presented with 3 weeks of abdominal pain and OGIB.

Interventions and Outcomes: Patient underwent usual endoscopic modalities in identifying the source of her gastrointestinal bleeding. Computerized tomography scan identified intussusception of the SB; however, conventional endoscopy and CE were negative for etiology of source of bleeding. Ultimately, DBE successfully located the site of gastrointestinal bleeding, confirmed by pathology as a leiomyosarcoma of the SB.

Discussion: Conventional endoscopy and CE may miss some lesions, while DBE can navigate altered SB anatomy, take biopsies, and even provide therapy to the lesion. Although double balloon enteroscopies are expensive and require longer sedation than average endoscopic modalities, they may provide another tool for the diagnosis of SB lesions when other modalities are unsuccessful.

Keywords: leiomyosarcoma; double balloon enteroscopy; small bowel tumors; balloon-assisted enteroscopy; deep enteroscopy; capsule endoscopy.

INTRODUCTION AND PATIENT PROFILE

Small bowel (SB) tumors are rare, accounting for 1–5% of all malignant gastrointestinal tumors; leiomyosarcomas constitute a small percentage of SB tumors (exact numbers are not known), with SB tumors having an incidence of 22.7 cases in 1 million per year.1,2 Leiomyosarcomas are a type of soft tissue sarcoma that arise from mesenchymal malignant cell lines.3 They can originate from smooth muscle cells lining blood vessels or from viscera, including the gastrointestinal tract or uterus.3 Patients with SB leiomyosarcomas generally present with non-specific symptoms of abdominal pain, gastrointestinal bleeding, or a palpable mass, manifesting most commonly in the sixth decade.1 These tumors present with late symptoms and are difficult to detect.2 Due to high mitotic activity, early diagnosis of leiomyosarcoma is crucial to prevent metastasis to other organs. There are three classes of leiomyosarcomas: Ia and Ib, Ia and IIb, and III; I signifying low histologic grade; II, medium histologic grade; and III, high histologic grade. Letters ‘a’ and ‘b’ define whether the tumor is confined to the gastrointestinal tract or unconfined (metastatic activity), respectively. Class III is associated with metastatic lesions. Studies have shown a 79–93% death rate in untreated patients with a leiomyosarcoma greater than 10 cm in size.4

Current techniques available to diagnose leiomyosarcomas include computed tomography (CT) enterography, positron emission tomography (PET) scans, video capsule endoscopy (CE), and/or double balloon enteroscopy (DBE). Traditionally, identifying the source of gastrointestinal bleeding involves CT scan, PET scan, and most importantly CE. The majority of cases do not require the use of DBE; however, many tertiary hospitals carry this modality when other endoscopic techniques fail to confirm the source of obscure gastrointestinal bleeding (OGIB), as seen in the case below. CE involves the patient swallowing a pill-sized camera to facilitate visualization of gastrointestinal anatomy (Fig. 1).5

Conventional endoscopic techniques such as CE are purely diagnostic tools unlike deep enteroscopy
methods such as balloon assisted enteroscopy or spiral enteroscopy, which are both diagnostic and therapeutic (e.g., polyp removal, hemostasis, and dilatation). DBE, first discovered in 2001, often follows CE to confirm a SB lesion or detect the site of bleeding that a CE may have missed. This procedure (DBE) involves a “push-pull” technique in which two balloons are inflated and deflated sequentially to allow pleating of the SB and advancement of the enteroscope. The system has a long enteroscope (200 cm) and overtube (150 cm), and a balloon at the distal end of the enteroscope and overtube, allowing deeper intubation of the SB (Fig. 2). DBE is a safe and practical method to investigate the SB with a complication rate of approximately 1.2% (up to 3% with altered SB anatomy). Disadvantages of DBE include the high cost of the instrument, thus making the procedure cost-prohibitive for many patients as well as unavailable at smaller gastrointestinal clinics. In addition, the length of the DBE procedure requires that the patient undergo prolonged anesthesia.

This case report highlights the advantageous role of DBE as a diagnostic tool in a patient who presented with OGIB and a SB intussusception, eventually discovered to have a SB leiomyosarcoma.

A 46-year-old Caucasian female presented at the hospital with complaints of generalized abdominal pain of three weeks duration. She described her pain as being intermittent, of moderate severity and non-radiating, and unrelated to food ingestion. In addition, she had noted four episodes of black tarry stools in the preceding week suggestive of melena.

Her previous medical history revealed that she was healthy prior to this episode without any medical issues. Family history was negative for malignancies including colon and digestive tract tumors. The patient ate a regular diet and had no toxic habits including smoking, alcohol use, or substance use.

Upon physical examination, her abdomen was soft, non-tender, with normal bowel sounds without palpable organomegaly. Abnormalities detected on her laboratory data revealed microcytic anemia with a hemoglobin level of 11 g/dL. Fecal hemoccult test was positive.

**INTERVENTIONS AND OUTCOMES**

A CT enterography revealed a 17 cm jejunojejunal intussusception in the left lower abdomen and upper pelvis along with 3.5 cm dilation of proximal jejunal loops. There was no lead point or mass lesions seen. Upper and lower endoscopies subsequently followed by a CE were negative for an etiology and source for suspected blood loss. The patient then underwent an antegrade DBE, which revealed a friable, 4.5 cm ulcerated mass with visible bleeding in the proximal jejunum at approximately 120 cm from the ligament of Treitz (Fig. 3A, 3B). Pathology identified features consistent with malignant spindle cell neoplasm confined to the
gastrointestinal tract without metastasis. The tumor was defined with fascicles of spindle-shaped cells, each of which contained oval or polygonal shaped nuclei (Fig. 4). Differential possibilities at this point in time included gastrointestinal stromal tumor versus a leiomyosarcoma. Ultimately, the presence of high ulceration on the mucosal surface accompanied with high mitotic activity of 15 mitosis per high-power field supported a histopathologic diagnosis of leiomyosarcoma (Fig. 4).

Further staging suggested a localized tumor without evidence of lymph node involvement or metastasis. A curative resection was performed 1 month after diagnosis. Her post-operative course was uncomplicated with expeditious recovery. Subsequent follow-up visits with periodic PET/CT scans did not show any evidence of relapse. A program of observation with periodic PET/CT scans was implemented to monitor future problems or recurrence.

DISCUSSION
Leiomyosarcoma is a rare but aggressive malignant tumor of the SB that has the potential for both lymphatic and hematogenous spread. Early diagnosis decreases mortality and improves prognosis. Diagnosis, however, can be challenging with most conventional endoscopic modalities.

The initial diagnostic approach to a patient presenting with OGIB would be an upper GI endoscopy, colonoscopy, and push enteroscopy followed by CE and angiography, if clinically indicated. Since 2001, CE, also known as Pillcam®, has proven to be an effective tool in detecting OGIB as well as identifying masses in the small and large bowel. CE may miss OGIB sources in 19% of tumors and malignancies. In addition, 9.8–17% of patients with SB tumors may be at risk of retaining the capsule endoscope. It is important that patients undergo both CE as well as DBE procedures to affirmatively establish a diagnosis. Although CE can identify locations of lesions and occult gastrointestinal bleeding sources, they are incapable of obtaining biopsy specimens or performing therapeutic interventions. As demonstrated in the patient above, if a CE is non-diagnostic, a DBE may not only detect lesions that a CE may have missed but can also assist in obtaining biopsy specimens. Therefore, DBE may improve the diagnostic yield with a lower complication rate.

DBE is a useful adjunctive diagnostic procedure if other modalities such as CE or CT enterography fail to establish a diagnosis. Furthermore, DBE may localize the SB tumor and perform therapeutic interventions.
including polypectomy, stricture dilation, and hemothysis. In addition, the ability of double balloon enteroscope to navigate sharp turns of the intestine makes it a superior technique for people with altered SB anatomy.

In conclusion, this case report highlights a patient with OGIB, the source of which was not detected by video CE. The use of DBE has been verified to be a preferable follow-up diagnostic technique in early discovery of gastrointestinal masses, as in this case, ultimately confirming a histopathologic diagnosis of malignant leiomyosarcoma.

LEARNING POINTS

1. SB tumors account for 1–5% of all gastrointestinal malignancies, and leiomyosarcomas are a rare etiology of the SB tumors.
2. Early diagnosis is crucial to improve survival in light of its potential propensity for aggressive lymphatic and hematogenous spread.
3. Conventional diagnostic modalities, such as CE, may miss SB tumors and are unable to therapeutically treat gastrointestinal lesions.
4. DBE can detect lesions missed by CE and are able to navigate altered SB anatomy while performing therapeutic interventions unlike conventional endoscopic techniques.

Conflict of interest and funding: The authors have nothing to disclose and state no source of support.

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8. Gill M. Double balloon enteroscope and overtube. March 28, 2014. Licensed under Creative Commons Attribution 4.0 International License CC BY NC SA.
Isolated Orbital Mucormycosis in an Immunocompetent Adolescent

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Introduction and patient profile: Mucormycosis is a life-threatening disease that usually affects patients with diabetes and other immunocompromised states. However, recent literature has shown an emergence of this disease in immunocompetent individuals. Here we are presenting a rare case of a healthy 13-year-old adolescent diagnosed to have isolated orbital mucormycosis, previously treated with oral and intravenous corticosteroids. The patient presented with a chief complaint of left eye swelling of 3 weeks’ duration, which progressed to proptosis and a visual acuity of no light perception.

Interventions and outcomes: Diagnosis of mucormycosis was done using histopathological techniques supported by radiologic imaging. Successful treatment of mucormycosis was achieved via amphotericin B administration and orbital exenteration in this case.

Discussion: The use of corticosteroids may weaken the immune system of healthy patients and can cause rapid progression of the disease. Early clinical diagnosis is important because this infection can rapidly be fatal.

Keywords: rhinocerebral; zygomycosis; pediatric; amphotericin B; corticosteroids; exenteration.
mucormycosis such as eschar formation and imaging did not show frank invasion of the left orbit from the focal sphenoid sinusitis. A 13-year-old male from the rural and grassy areas of provincial Philippines, with no known comorbidities, presented with a chief complaint of swelling of the left eye of 3 weeks’ duration. The swelling progressed to a slight protrusion of the affected eye. He also noted difficulty raising the eyelid, blurring of vision, diplopia, and limited horizontal movement. The patient consulted a private ophthalmologist where he was prescribed unreccalled eye medication for 4 days, which provided no relief. A week after the first consult, the swelling progressed and the patient consulted another ophthalmologist who prescribed oral prednisone 50 mg/tablet once a day, which provided 10% subjective minimal improvement. His symptoms persisted for another week with continued prednisone treatment, which prompted admission to a local hospital. The patient was treated with oral prednisone 50 mg/tablet increased to twice a day and intravenous amoxicillin–clavulanate. He was discharged after 5 days, with improvement of the affected eye noted by his ability to raise his eyelids, absence of diplopia, and no horizontal limitation. He was advised to continue oral medications and consult an orbit specialist of choice. At follow-up, there was no further improvement, leading to admission at the author’s institution soon after.

**INTERVENTIONS AND OUTCOMES**

Upon admission, the patient was noted to have proptosis of the left eye, with visual acuity of 20/20 – 1, J + 1. The right eye had a visual acuity of 20/20, J + 1. Initial therapeutics included oral prednisone 20 mg/tablet twice a day, amoxicillin–clavulanate 625 mg/tablet twice a day, and intravenous methylprednisone 1 g bolus per day for 3 days. On the first hospital day, the patient had diplopia on all gazes and pain on lateral gaze of the left eye. A computed tomography (CT) scan done on the same day showed a soft tissue density in the medial aspect of the left orbit with periorbital swelling and focal left sphenoid sinusitis. After the first dose of methylprednisone on the patient’s second hospital day, the left eye was notably less erythematous, but still slightly proptosed. A complete blood count revealed increased WBC (26.3 x 10^9/L) predominantly neutrophilic (95%), suggesting acute bacterial infection, inflammatory type. An elevated white count could result from the methylprednisone administered to the patient.

By the third hospital day, another CT scan showed a slight decrease in size of the mass-like lesion. The patient experienced left-sided headache (pain scale 9/10) the following day. His left eye was hyperemic and proptosed with a visual acuity of 20/30 – 1; right eye had a visual acuity of 20/20 J + 1. The patient was given acetazolamide 250 mg/tablet for the headache. Intraocular pressure on the left was initially at 19 mmHg and was brought down to 10 mmHg 1-hour post-acetazolamide; right eye intraocular pressure remained at 10 mmHg. Two days later, he still had a persistent headache (pain scale 9/10) for which he was given tramadol 50 mg IV. His left eye was erythematous, swollen, and proptosed with no light perception (NLP). His left pupil was fixed at 5 mm; right eye had a visual acuity of 20/20, J + 1, full extraocular movements with pupils at 2–3 mm reactive to light. On fundoscopy, the left eye had a pale retina and loss of cupping with blurring of disc borders.

By the sixth day of hospitalization, his left eye was swollen, proptosed, with NLP. Left pupil was fixed at 6 mm with negative extraocular movements. The patient was started on mannitol 150 ml every 6 hours, and underwent an emergency left orbital exploration and decompression with tumor debulking with subsequent transfer to the pediatric intensive care unit. On the following day, his headache decreased in intensity (pain scale 5/10); however, the left eye was still proptosed with NLP. A complete blood count showed a drop in white blood cells (13.5 x 10^9/L) from previous count (26.3 x 10^9/L), predominantly neutrophilic (85%). Magnetic resonance (MR) imaging done on the same day (refer to Fig. 1) revealed a large peripherally enhancing mass primarily located along the extraconal compartment of the left orbital cavity causing marked proptosis of the left globe. There were also multifocal cortical signal abnormalities involving the high frontoparietal regions bilaterally, associated with adjacent leptomeningeal contrast enhancement.

On the eighth day of admission, the patient still had periorbital pain (pain scale 3–4/10) with blood pressure elevations (140–150/100–110) that required clonidine and a nicardipine drip. The patient’s condition failed to improve despite tumor debulking and continued antibiotics (refer to Fig. 2) the following day. He was then referred to pediatric infectious disease where a clinical diagnosis of fungal infection was made. Amphotericin B was started at 0.75 mg/kg (36 mg IV) and nicardipine drip was increased for the ongoing high blood pressure.
The patient underwent a left orbital exenteration with removal of the left eye, adnexa, and part of the bony orbit under the impression of a rapidly invasive fungal infection on his tenth day of admission. Gram stain showed positive *Mucor spp.* from the orbital mass specimen. A lumbar puncture was obtained and the cerebrospinal fluid specimen submitted on this day showed negative growth of *Mucor spp.* after 5 days.

However, pathology results revealed filamentous, non-septated, broad fungus morphologically consistent with *Mucormycosis spp.* involving periorbital soft tissue, optic nerve, and intraocular structures. This was also associated with panophthalmitis with retinal detachment, hemorrhage, and subconjunctival hemorrhage. The tissue was also positive for necrosis and infarction.

On the thirteenth day of hospitalization, the patient had no pain in the left eye socket, the dressing was moderately soaked with serosanguinous fluid and he had a normalizing blood pressure. A complete blood count performed on Day 19 demonstrated a continued normalization of white blood cells (12.8 × 10⁹/L), predominantly neutrophilic (85%).

In summary, the patient was treated with left orbital exenteration and completed 26 days of amphotericin B. He made steady improvements and was discharged after 39 days in the hospital.

**DISCUSSION**

*Mucormycosis* is a life-threatening disease that usually affects patients with diabetes, prolonged corticosteroid use, hematologic malignancies, chronic renal failure, and other immunocompromised states.⁴ A study reporting the epidemiology of zygomycosis shows that the mean age of patients affected was 38.8 years, 65% male. The most common types of infection affected the sinuses (39%), pulmonary organs (24%), cutaneous (19%), and dissemination developed in 23% of cases.¹⁰

Presentation of this disease greatly varies in terms of organs affected and whether or not it would take an indolent or rapid course. In this case, the patient exhibited a rapid progression of the disease despite his previous healthy status. However, the patient was put on corticosteroids for approximately 1 month, thus contributing to immunosuppression. Rapidly progressive rhinocerebral mucormycosis has been reported after a course of prednisone therapy (40–80 mg/day) in an elderly patient with controlled diabetes,¹¹ suggesting that corticosteroids increase the risk of developing mucormycosis. Another study reported the development of *Rhizopus microsporus* infection in a patient with mild steroid-induced hyperglycemia.² It was deduced that the fungus received nourishment from elevated glucose levels in the body¹¹ supporting the prevalence of mucormycosis in patients with poorly controlled diabetes.¹² Corticosteroid treatment affects the ability of mouse bronchoalveolar macrophages to prevent the germination of spores in vitro or after in vivo infection induced by intranasal inoculation.¹³

Chronic corticosteroid based therapy therefore presents...
as a risk factor by causing defects in macrophages and neutrophils and/or steroid induced diabetes.\(^9\)

Orbital involvement results from invasion of the nasolacrimal duct spreading through the thin medial orbital wall. This usually presents with proptosis and medial rectus thickening.\(^12\) The initial symptoms of rhinooorbitocerebral mucormycosis are consistent with those of sinusitis and periorbital cellulitis. This may include eye and/or facial pain and facial numbness, followed by blurry vision. Other symptoms include multiple cranial nerve palsies, unilateral periorbital facial pain, orbital inflammation, eyelid edema, blepharoptosis, proptosis, acute ocular motility changes, internal or external ophthalmoplegia, headache, and acute vision loss.\(^9\) Although this patient had minimal signs of sphenoid sinusitis, there was no break in the mucosa to indicate direct spread from the sinuses. There was no eschar or signs of fungal invasion in the nose. However, eschar is present in only 20%–30% of patients.\(^12\) It is theorized that the patient may have inhaled this ubiquitous saprophytic organism while living in a grassy rural area.

In immunocompetent patients, the nose and/or maxillary sinuses appear to be the predominant source of infection of the respiratory tract. If sporangiospores are larger than 10 \(\mu m\), they may remain localized to the upper airways, giving an isolated form. Otherwise, they may colonize the distal alveolar spaces involving the pulmonary tract. Once infection has colonized the nose and paranasal sinuses, it should be promptly diagnosed and treated. If there is a delay, infection may invade the base of the skull through blood vessels, disseminating to the central nervous system, giving the rhinoorbitocerebral form, as seen in this case.\(^8\) Since the mucosal epithelium and endothelium serve as effective barriers against tissue and angioinvasion, \textit{Mucor} infection in such patients seems to be attributed to the ability of the fungus to attack the epithelium previously damaged by prior infection, cytotoxic agent, or direct trauma. It is likely that \textit{Mucor} sporangiospores secrete several toxins or proteases that destroy endothelial cells in mucosal membranes.\(^14\)

It has been hypothesized that a chronic local insult, such as chronic sinusitis, might act as a predisposing factor for possible development of \textit{Mucor} infection in immunocompetent individuals. There is a disruption of the first-line barrier defense of upper airway caused by an impaired mucociliary clearance.\(^8\) In addition, patients with chronic sinusitis have a reduction in several molecules involved in the epidermal differentiation complex, such as S100 and SPINK5, which are necessary in maintaining the barrier function of the upper airways and sinuses.\(^15\) The patient in this case showed signs of sphenoid sinusitis. It is unclear whether this was an acute or chronic insult; however, it is hypothesized that the \textit{Mucor} infection spread to the orbital region from the sphenoid sinus.

Survival depends upon early diagnosis and adequate treatment. As the disease progresses beyond the boundaries of the sinuses, orbit, brain, skin, or lung, the prognosis worsens.\(^1\) The earliest sign of infection is facial edema followed by proptosis, chemosis, and extracocular muscle paresis. Other manifestations include perinasal cellulitis, paresthesia, periorbital edema, mucopurulent rhinorrhea, and nasal crusting.\(^6,9,10,12\) Early diagnosis of mucormycosis and initiation of appropriate therapy within 5 days has a survival rate of 83% compared with a 43% survival rate at greater than 5 days.\(^5\) Pre-operative contrast enhanced CT is useful in defining the extent of the disease which would show edematous mucosa, fluid filling the ethmoid sinuses, and destruction of periorbital tissues and bone margins. MR imaging is useful in identifying intradural and intracranial extent of the infection. Contrast-enhanced MR imaging can also demonstrate perineural spread. However, imaging studies are not confirmatory tests for mucormycosis. Diagnosis should be made via histopathological identification of fungal tissue invasion. \textit{Mucorales} is identified by culture and microscopic visualization of broad, non-septated hyphae.\(^9\)

Treatment is a combination of systemic amphotericin B at the highest tolerable dose,\(^1,3,5,7,10–13\) orbital debridement, and adjacent tissue debridement.\(^1,4,5,7,10–13\) A survival rate of 70% was attributed to cases treated with antifungal and surgical management; 61% for cases treated with amphotericin B deoxycholate only; 57% for cases treated with surgical management only; and 3% for cases that were not treated.\(^8\) Blood vessel thrombosis and resulting tissue necrosis prevents the penetration of the anti-fungal medications. Therefore, surgical debridement greatly improves survival.\(^13\)

In conclusion, although mucormycosis commonly affects immunocompromised patients, there have been emerging reports of this rare disease among healthy individuals, as is the case presented here. The initial symptoms of rhino-orbico-cerebral mucormycosis are consistent with those of sinusitis and periorbital cellulitis. As the infection spreads, it can manifest as headaches, proptosis, ophthalmoplegia, acute vision loss, and multiple cranial nerve palsies.\(^9\) This can be a rapidly fatal infection, and timely diagnosis and aggressive treatments are therefore essential. Although
imaging studies are used to determine the extent of involvement, definitive diagnosis is done by a biopsy, which will show broad, non-septated hyphae. Mucormycosis is adequately treated with amphotericin B and surgical debridement. In retrospect, the administration of steroids during the initial presentation of the patient could have weakened the immune system and may have accelerated the rate of invasion. As presented above, the use of corticosteroids over a long period of time is a risk factor for the development of mucormycosis.

LEARNING POINTS

1. Clinical diagnosis is important because this infection can rapidly be fatal. Early diagnosis of mucormycosis and initiation of appropriate therapy within 5 days has a survival rate of 83% compared with a 43% survival rate at greater than 5 days.
2. Mucormycosis infection is most commonly seen in immunocompromised patients, but can also occur in immunocompetent individuals, and even including those on chronic steroids, with hematological malignancies, or with chronic kidney disease.
3. Although imaging can determine the extent of the infection, a confirmatory diagnosis is done with a biopsy showing broad, non-septated hyphae.
4. Judicious use of steroids is emphasized because it can accelerate the speed of invasion of mucormycosis.
5. Successful treatment of mucormycosis involves both amphotericin B and surgical debridement leading to increased survival with the combination.

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