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Two Cancers Arising from Different Mesenchymal Origins: An Unexpected Connection over Time and Space

Natascha Putri¹, Sze Min Lek¹, Nicholas Brian Shannon¹, Joey Wee-Shan Tan¹, Grace Hwei Ching Tan¹, Clara Mae Shulyn Chia¹, Melissa Ching Ching Teo¹, Choon Hua Thng², Timothy Kwang Yong Tay³, Chin-Ann Johnny Ong⁴*, Tina Puay Theng Koh⁴*

¹Division of Surgical Oncology, National Cancer Centre Singapore, Singapore City, Singapore
²Division of Oncologic Imaging, National Cancer Centre Singapore, Singapore City, Singapore
³Department of Anatomical Pathology, Singapore General Hospital, Singapore City, Singapore
Email: *tina.koh.p.t@singhealth.com.sg, *johnny.ong.c.a@singhealth.com.sg

Abstract

Sarcomas are rare tumours, accounting for 1% of all malignancies. They are histologically diverse, presenting with more than 50 different subtypes. Sarcoma can be broadly divided into two categories—soft tissue sarcoma and bone sarcoma. Extraskeletal osteosarcoma is a unique subtype which is histologically similar to bone osteosarcoma but resides within soft tissue and has no attachments to bone. We present a rare case of a patient who initially presented with an extraskeletal osteosarcoma that was complicated by a chronic chest wall sinus and lymphedema of the left arm. He later developed enlarging left chest wall nodules at the same region that were proven to be dedifferentiated liposarcoma on biopsy 20 years later. We examine the occurrence of both extremely rare diseases of differing pathologies over the same site but separated by an extraordinarily long interval, and possible new associations to account for this phenomenon.

Keywords

Sarcoma, Extraskeletal Osteosarcoma, Dedifferentiated Liposarcoma, Osteogenic Sarcoma

1. Introduction

Sarcomas are rare and uncommon tumours, representing 1% of adult malignancies [1]. They are a heterogeneous group of tumours of mesenchymal origin that can occur anywhere in the body. Sarcomas are broadly divided into two catego-
ries—soft tissue sarcoma and bone sarcoma, of which liposarcoma and osteosarcoma are the most common histological subtypes respectively.

Extraskeletal osteosarcoma is a unique subtype of sarcoma, presenting with similar histology to that of osteosarcoma but lies within soft tissue and is not attached to any bones [2]. It represents approximately 1% - 2% of all soft tissue sarcomas, and behaves aggressively, carrying mortality rates up to 80% [3]. Extraskeletal osteosarcomas are different from its primary counterpart of osseous origin—it occurs rarely in the younger population, and are poorly responsive to chemotherapy, with local and distant failures in more than 80% of those affected. Disease-free intervals have been found to range from two months to ten years [4]. Specifically, primary thoracic extraskeletal osteosarcoma is even rarer, and only 60 cases have been reported to date with the most common presentation coming from the lungs. The prognosis is usually extremely bleak, as the majority of patients reported had demised within months due to rapid disease progression, and overall survival at 1 year stands only at 41.8% and decreases to 22.3% at 5 years [5].

Herein, we report an interesting case of a patient who underwent resection for extraskeletal osteosarcoma 20 years ago and recently presented with a dedifferentiated liposarcoma at the same site.

2. Case Summary

Our patient is an 81-year-old Chinese male with comorbidities of hypertension and hyperlipidemia and a significant smoking history. He previously received treatment in another hospital for a left chest wall extraskeletal osteosarcoma for which he underwent wide excision and reconstruction with mesh and latissimus dorsi flap in 1997. He did not receive further adjuvant treatment. He remained well and disease-free until 2016 when he noted a persistent chronic chest wall sinus as well as left upper limb lymphedema that had failed conservative management. Computed tomography scan of his chest showed a 2.7 cm soft tissue thickening over the left anterior chest wall surgical site with no evidence of pulmonary metastasis or vascular obstruction. Clinical examination revealed no visible or palpable nodules, and incisional biopsy of the chest wall sinus proved to be inflamed granulation tissue with no evidence of malignancy or any infective organisms. He declined further investigations for possible disease recurrence then and only consented to treatment for the left upper limb lymphedema. He underwent left upper limb lymphovascular anastomosis in 2017 with good results. A repeat computed tomography scan of his chest done in 2018 showed interval stability of the soft tissue density, as well as oedematous changes present over the left anterior and lateral chest wall muscles. There were no overt masses detected.

However, in early 2019, his symptoms recurred with worsening lymphedema of the left upper limb associated with left chest wall nodularity inferior to the previous reconstruction site that was suspicious of underlying recurrence. He was otherwise well with no other systemic symptoms. On examination, our pa-
A patient had a few clusters of non-tender, hard nodules on the left lateral chest wall at the angle of the ribs just below the nipple with no surrounding erythema or ulcers (Figure 1(a) and Figure 1(b)). A long well healed scar extending from the anterior chest wall to the scapular region is seen, the left clavicle was previously surgically resected and the infraclavicular fossa is depressed relative to the right. There is marked winging of the scapula but the patient retained a good range of movement of his left upper limb. There was no cervical or axillary lymphadenopathy bilaterally. Of note, there is marked lymphedema of the left upper limb. At the midsternal region, there is a small chronic chest wall sinus (Figure 1(c)).

A magnetic resonance imaging scan of the chest was performed which showed enlarging clusters of enhancing soft tissue nodules located at the region of the previous left latissimus dorsi flap repair in the intermuscular fascial plane (Figure 2). There was progressive increase in size of the left chest wall nodularity, but no intraosseous abnormality or gross destruction of the bones. He underwent ultrasound-guided biopsy of the left chest wall mass, and histopathology revealed the lesions to be dedifferentiated liposarcoma, which was MDM2 positive (Figure 3). This case was discussed at the multi-disciplinary tumour board meeting and curative surgical resection proposed. However, the patient declined surgery in view of his current relatively well state and elected to continue monitoring during his last review three weeks ago. He will be due for follow-up in a month.

**Figure 1.** (a) and (b)) Photograph of lateral chest wall of patient demonstrating presence of nodules with no surrounding erythema or ulcers at the site of latissimus dorsi flap; (c) Photograph of chronic discharging sinus at mid sternal region.

**Figure 2.** Magnetic resonance imaging scan of (a) transverse plane and (b) coronal plane showing cluster of enhancing soft tissue nodules in the region of the left latissimus dorsi flap.
3. Discussion

Among soft tissue sarcomas, liposarcoma is the most common and accounts for approximately 20% of all cases [6]. These tumours affect adults with a peak incidence at around 60 years of age. About 10% progress to dedifferentiated liposarcomas and is most commonly non-lipogenic and pleomorphic. Heterologous differentiation can occur in 10% of dedifferentiated liposarcomas and present with myogenic, osteo- or chondrosarcomatous or angiosarcomatous components.

Extraskeletal osteosarcoma is a rare entity that accounts for 1% - 2% of all soft tissue sarcomas and 6% of all osteosarcomas. They too occur typically in the elderly with a predilection to the extremities and retroperitoneum. It is a malignant mesenchymal tumour that directly produces neoplastic osteoid or bone and diagnosis requires a careful exclusion of heterologous osteosarcomatous differentiation arising in a variety of malignant neoplasms.

This is an interesting case whereby the surprise diagnosis of dedifferentiated liposarcoma in this current instance raises several unique and rare possibilities; whether the current presentation is a recurrence linked to the previous history of extraskeletal osteosarcoma, or a de novo occurrence of a second primary malignancy arising from cells of a different mesenchymal origin. Another possibility could be a misdiagnosis in the index presentation, where for instance, the initial tumour could have been a dedifferentiated liposarcoma all along, but only the predominant osteosarcomatous component was reported.

To our knowledge, there are no published anecdotes of two different primaries of these unrelated mesenchymal cell types, arising in the same patient at the same site spaced twenty years apart, which makes this novel case noteworthy. One predisposing factor which could have led to the development of a secondary malignancy is the chronic inflammation from the persistent sinus tract or upper limb lymphedema. However, what is reported in literature so far have been lymphangiosarcomas such as in the case of Stewart-Treves syndrome [7], and no association with dedifferentiated liposarcoma has been demonstrated before.

Alternatively, if this new tumour is a recurrence arising from his initial disease, the extremely long disease-free interval and the disparate mesenchymal
cells of origin would make this case highly unusual. Osteogenic sarcomas have very poor prognosis with 5-year overall survival rates being reported as low as 11.7% [2] [8] [9] [10]. The established natural history of dedifferentiated liposarcomas, where 90% arise de novo while only 10% occur in recurrence, also run contrary to this current presentation [11] [12]. There have been no documented cases in existing literature describing this condition to date.

Another unlikely explanation calls into question the initial diagnosis of extraskeletal osteosarcoma established 20 years ago. The use of molecular markers to distinguish the various sarcoma subtypes has started to become available only recently, such as MDM2 and CDK4 positivity being pathognomonic of liposarcoma. In the absence of MDM2 testing and histopathological review being performed on the first tumour specimen obtained years ago, this opens the possibility of the original diagnosis being a dedifferentiated liposarcoma with osteogenic components being erroneously identified as the primary malignancy. Although uncommon, there have been sporadic case reports describing dedifferentiated liposarcomas with osteosarcomatous components or dedifferentiation to osteosarcoma [13] [14]. In this hypothetical situation, it is also remarkable for dedifferentiated liposarcoma to remain dormant and only recur two decades later, as the known mean time to recurrence is often within two years [1].

4. Conclusion

This case emphasizes the need for continued vigilance in the surveillance of sarcoma patients as the disease may have an unprecedentedly long disease-free interval. More importantly, it also exposes the gaps in our current understanding about the behavior of osteosarcomas and dedifferentiated liposarcoma as the temporal sequence of this presentation runs contrary to their established natural history. More can be done to expand the role of molecular markers to distinguish the various subtypes so as to identify the exact mesenchymal cell of origin for these rare tumours and determine the optimal treatment required.

Conflicts of Interest

The patient provided written informed consent for the publication of this case report and its accompanying images.

References


Infective Endocarditis in Tetralogy of Fallot Complicating Brain Abscess—A Case Report

Ramachandran Muthiah
Port Trust Hospital, Thoothukudi, India
Email: cardioramachandran@yahoo.co.uk

Abstract

Aim: To report a case of solitary, parietal lobe abscess in a boy, aged 16 years in Tetralogy of Fallot. Introduction: Infective endocarditis is a serious and fatal complication in congenital heart disease. Following bacterial endocarditis, ventricular septal defect (VSD) and Tetralogy of Fallot (TOF) have less morbidity and higher survival rate in children. Neurological complications were recognized in 20% of cases and brain abscess is a serious infection of brain parenchyma as a result of seeding of infective pathogens in the shunted blood from the right side of the heart. Case Report: A 16 year old boy had Tetralogy of Fallot, presented with altered sensorium of sudden onset. Echocardiography revealed a large vegetation, attached to the ventricular septum and a large VSD with overriding of aorta. CT brain revealed a large abscess cavity in the parietal lobe, which was evacuated by aspiration and treated with antibiotics. Conclusion: Any patient presented with altered sensorium in cyanotic congenital heart disease must be evaluated with CT scanning for brain abscess and also check hematocrit to rule out hyperviscosity syndrome. Lumbar puncture has been considered hazardous in patients with brain abscess and usually performed under a strong suspicion of meningitis or ventriculitis in the absence of increased intracranial pressure.

Keywords
Tetralogy of Fallot, Vegetation, Brain Abscess, Five Component Therapy, Surgical Aspiration

1. Introduction

Cyanotic congenital heart disease is characterized by intracardiac right-to-left shunting of unsaturated blood and its distribution into the systemic circulation resulting in arterial hypoxaemia, leading to pulmonary vasoconstriction, poly-
cythaemia, coagulopathy, infective endocarditis (IE) and brain abscess due to increased risk of paradoxical embolism. Cyanotic heart disease accounts for 12.8% - 69.4% of all cases of brain abscess with the incidence being higher in children [1] [2]. The risk of brain abscess complicating cyanotic CHD (congenital heart disease) is inconstant, but is more common after two years of age and increases consistently until the age of 12 years. Of all the patients with brain abscess and cyanotic congenital heart disease, TOF (Tetralogy of Fallot) is the most common in association (13% - 70%) of cases [3] [4] [5] [6] [7].

Infected endocarditis typically presents more insidiously in patients with congenital heart disease. The risk of infected endocarditis in cyanotic CHD is more than six times the risk compared to those in acyanotic CHD. Patients with congenital heart disease have structural changes that create turbulence and shear force in blood flow that disrupts the endocardium, exposing the subendocardial collagen and extracellular matrix. The resultant inflammation causes endothelial cells to express β1 integrins, which bind circulating fibronectin to the endothelial surface and promote scar formation. During the healing process, production of tissue factor, deposition of fibrin, and platelet adherence lead to hemostasis and pathogenic organisms may settle in and infect the endocardium in these scarred areas. With sequestration and limited blood supply to a damaged area, formation of vegetation and/or abscess may occur. These friable vegetations have the capability of causing emboli, which may cause distal abscess formation, especially in the brain and so this case had been reported.

2. Case Report

A 16 year old cyanotic male was admitted with altered sensorium in the intensive care unit. He was diagnosed as Tetralogy of Fallot and advised corrective surgery earlier. He was afebrile and his pulse rate was 64 bpm and blood pressure 100/60 mmHg. He had headache, vomiting episodes and stiff neck for the past 3 days. Blood chemistry revealed normal. ECG and X-ray chest as in Figure 1 (boot-shaped heart) were consistent with Tetralogy of Fallot. Physical examination revealed uniform central cyanosis with clubbing, 2/6 systolic murmur in the left second intercostal space and a single second sound. Echocardiography revealed a non-restrictive, large, malaligned VSD (ventricular septal defect), biventricular aorta as shown in Figure 2. A large vegetation was attached to the crest of interventricular septum (IVS) as in Figure 3 and Figure 4.

CT (computed tomography) brain revealed a large abscess cavity in the parietal region as in Figures 5-7. The abscess was aspirated via burr-hole and cultures were found to be negative. He was given ceftriaxone 1 g IV twice daily, amickacin 500 mg IV twice daily with tablet phenytoin sodium 100 mg twice daily for 2 weeks. He was symptom free and advised periodic follow up.

On 1 year follow up, the patient was asymptomatic without any sequelae and advised corrective surgery for the cardiac anomaly at the earliest.
Figure 1. X-ray chest PA (Postero-anterior) view showing the "boot-shaped heart" (arrow) of tetralogy of Fallot with oligemic lung fields in a 16 year old boy.

Figure 2. Showing the large, malaligned VSD (ventricular septal defect) of Tetralogy of Fallot in a 16-year old boy.
Figure 3. Showing “the vegetation” (arrow) attached to the crest of IVS (interventricular septum) in a 16-year old boy with Tetralogy of Fallot.

Figure 4. Showing “the vegetation” (arrow) seen across the VSD (ventricular septal defect) in a 16-year old boy with Tetralogy of Fallot.

3. Discussion

Review of Literature

Rushani and colleagues found that 34% of children with infective endocarditis had cyanotic CHD [8]. Elder and Baltimore found that infective endocarditis represented 0.05 to 0.12 per 1000 pediatric admissions. Tetralogy of Fallot (TOF) was described in 1888 by the French physician Etienne-Louis Arthur Fallot [9]. In 1814, Farre [10] discussed a case of tetralogy of Fallot in a boy aged 9 years who died of brain abscess. Lallemand Louis and Berthody [11] described similar cases and in 1880, Ballet reviewed the literature of it. Abbott and her collabora-
tors [12] reported two cases in 1923 and Rabinowitz and associates [13] were the first to report a case with correct antemortem diagnosis in 1932. Wechsler and Kaplan [14] described two cases in 1940.

**Etiopathogenesis**

TOF accounts for 10% of all cases of congenital heart disease [15] and the incidence of brain abscess in population with congenital heart disease varies from 5% to 18.7% [16]. In Fallot’s tetrad, Bing and associates [17] have shown that the shunting from right-to-left occurs in the absence of failure, owing to the overriding of aorta. When a reversal of flow is said to occur, favouring paradoxical embolism and paradoxical brain abscess stands second only to bacterial endocarditis.

Acute infective endocarditis is a tumultuous, destructive infection frequently involving a highly virulent organism such as staphylococcus or pseudomonas. Staphylococcus aureus is pervasive, with fibronectin binding protein on its surface. When integrins are exposed, they provide adhesion for circulating staphylococci which may also infect normal undamaged endocardium and once adherent, staphylococcus aureus internalizes and escapes host defences. Subacute infective endocarditis is “benign” with a typically more indolent course, often more than 6 weeks, and usually involves a less virulent organism such as streptococci infecting an anatomically damaged heart. Some viridans group streptococci have a type 1 fimbrial subunit that is a major adhesive protein to fibrin platelet aggregates.

Pulmonary circulation represents a potential filtering apparatus for systemic bacterial pathogens. In patients with right-to-left shunts, absence of pulmonary phagocytic clearance of pathogens can occur and the ischemic injury from hypoxaemia and polycythemia, produce low perfusion areas (microinfarcts) in the brain which may act as a nidus for infection [18]. In the development of brain abscess, inoculation of an organism is required into the brain parenchyma in an area of devitalized brain tissue or in a region with poor microcirculation and the seeded microorganisms can sustain growth and multiply to form abscess. Altered blood brain barrier permeability can occurs and infections from any systemic source may lead to bacteremia and subsequent spread to brain parenchyma even in the absence of cyanotic heart disease.

Brain abscess begins with a localized area of inflammatory change referred to as cerebritis. This early stage of infection is characterized by increased blood vessel permeability without angiogenesis. When unrecognized, this process will progress to an immature capsular stage and then to brain abscess, a condition defined by an area of parenchymal infection containing pus encapsulated by a vascularized membrane. Histologically, there are four stages in brain abscess formation: early cerebritis (day 1 - 3), late cerebritis (day 4 - 9), early encapsulation (day 10 - 13) and late capsule stage (>14 days) [19]. About 2 weeks are required for encapsulation, which is usually less complete on medial or ventricular side due to poor vascular supply [20]. The brain abscess capsule serve to prevent the infective process from becoming generalized and it also creates within it an
inflammatory “soup” that may impede resolution of the infection.

The mode of entry of organism could be by contiguous (primary dental, sinus, ear infections, or mastoiditis) spread (14% to 58%), hematogenous (endocarditis, pulmonary infections such as pneumonia, empyema and abscess) dissemination (9% to 43%) from a distant site as investigated by Warrington in 1918 [21] or following trauma and invasive neurosurgical procedures (3% to 18%). The incidence of brain abscesses is about 8% of intracranial masses in developing countries, whereas, in Western countries, the incidence is about 1% - 2% [22]. The predisposing factors of brain abscess are shown in Table 1.

Several predisposing factors are casually related, but in 14% - 25% of patients, no cause can be found [25] [26].

A single organism is isolated in majority of bacterial brain abscess. Anaerobic streptococci are most common agents in cyanotic heart disease with brain abscess. However, isolation of multiple pathogens from abscess materials is not uncommon (4% - 23%) [27] [28]. Cultures are negative in 16-68% of brain abscess with cyanotic heart disease [29]. Administration of antibiotics prior to the collection of abscess material is often cited as the explanation for sterile culture. The abscess drained within 3 days of antibiotic administration had much greater yield than otherwise (84% and 32% respectively) [30]. Bacteroides fragilis and peptostreptococcus are the most common anaerobic organisms isolated [31]. Organisms vary significantly with the etiology of abscess as shown in Table 2 [32].

Individuals with AIDS having brain abscess are more likely to have multiple abscesses and tuberculous abscess. Toxoplasma encephalitis is the most common multifocal infectious process encountered in advanced HIV and this population is more susceptible to intracranial infections from Listeria, Cryptococcus, and Nocardia [33].

Fungal brain abscess mostly related to Aspergillus and other species including candida are common in organ transplant patients and immunocompromise raises the risk of CNS infection with an incidence as high as 37.5%.

Moyamoya disease, a vaso-occlusive disease of cerebral blood vessels with a number of collaterals at the base of brain giving a “smoke of puff” (“moyamoya” in Japanese) is rarely associated with TOF and presents with CNS involvement such as stroke and seizures [34] and may produce abscess in the brain.

Abscess can occur in any location of brain, which is closely associated with source [35]. Otogenic abscess occurs almost exclusively in the temporal lobe and

### Table 1. Showing the predisposing factors of brain abscess.

| Congenital heart disease with a right-to-left shunt [23] |
| Infections of middle ear, mastoid, paranasal sinuses, orbit, face, scalp, penetrating skull injury and comminuted skull fracture |
| Intracranial surgery including insertion of ventriculo-peritoneal shunts |
| Abnormal immune functions [24] |
Table 2. Showing the varying organisms with the etiology of abscess.

<table>
<thead>
<tr>
<th>Source</th>
<th>Most commonly cultured organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paranasal sinus infection</td>
<td>Streptococcus spp.</td>
</tr>
<tr>
<td></td>
<td>Staphylococcus spp.</td>
</tr>
<tr>
<td></td>
<td>Enterobacteriaceae (especially Hemophilus spp., Pseudomonas aeruginosa)</td>
</tr>
<tr>
<td></td>
<td>Proteus mirabilis</td>
</tr>
<tr>
<td>Otogenic infection</td>
<td>Streptococcus milleri group organisms</td>
</tr>
<tr>
<td></td>
<td>Streptococcus pneumoniae</td>
</tr>
<tr>
<td></td>
<td>Staphylococcus aureus</td>
</tr>
<tr>
<td>Dental infection</td>
<td>Streptococcus spp.</td>
</tr>
<tr>
<td></td>
<td>Bacteroides fragilis</td>
</tr>
<tr>
<td></td>
<td>Staphylococcus aureus</td>
</tr>
<tr>
<td></td>
<td>Staphylococcus epidermidis</td>
</tr>
<tr>
<td></td>
<td>Enterobacteriaceae (most commonly P. aeruginosa, Enterobacter spp.)</td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td>Staphylococcus aureus</td>
</tr>
<tr>
<td></td>
<td>Staphylococcus epidermidis</td>
</tr>
<tr>
<td></td>
<td>Enterobacteriaceae</td>
</tr>
<tr>
<td></td>
<td>(most commonly P. aeruginosa, Enterobacter spp.)</td>
</tr>
<tr>
<td>Neurosurgical procedure</td>
<td>Pseudomonas aeruginosa</td>
</tr>
<tr>
<td></td>
<td>Propionibacterium acnes</td>
</tr>
<tr>
<td></td>
<td>Streptococcus spp.</td>
</tr>
<tr>
<td>Hematogenous spread</td>
<td>Staphylococcus aureus</td>
</tr>
<tr>
<td></td>
<td>Streptococcus viridans</td>
</tr>
<tr>
<td></td>
<td>Klebsiella pneumoniae</td>
</tr>
</tbody>
</table>

cerebellum [36], while abscess associated with sinus infection is predominantly frontal [37] [38]. A significant proportion of individuals develop multiple abscesses (9.3% - 28%) [39] [40] [41].

**Echocardiographic Features**

The four components of TOF are ventricular septal defect (VSD), aortic override, right ventricular outflow tract obstruction and right ventricular hypertrophy. In unrepaired TOF, pathophysiology depends on the degree of RVOT obstruction. When obstruction of right ventricular outflow is mild to moderate and a fairly balanced shunt operates across VSD and the patient may not be cyanotic, called as “acyanotic” or “pink” tetralogy of Fallot. The patient may remain relatively asymptomatic until the balance between pulmonary and systemic circulation is disturbed.

Echocardiography plays a key role in the diagnosis of infective endocarditis (IE) in TOF. Vegetation may occur on pulmonary and tricuspid valves [42] and a large vegetation occluding the VSD had been reported [43]. In this patient, a large vegetation attached to the crest of interventricular septum was shown in Figure 3 and Figure 4.

**CT Imaging**

Brain abscess is an encapsulated inflammation and can be easily diagnosed by CT scan. The CT appearance of an abscess is that of a well defined hypodense area showing ring enhancement and accompanied by extensive perifocal edema and mass effect. The ring enhancement on the CT scan surrounding a central
necrotic cavity as in Figure 5 is an abscess. The appearance of enhancing rim, the capsule of the abscess enhances and it is variable. The rim is formed probably by collagen and inflammation due to free radicals and micro hemorrhages in the abscess. The abscess tends to grow towards white matter, away from the better vascularized grey matter, with thinning of the medial wall. The preferential deposits of collagen on the outer edge of the abscess are due to the vascularization of grey matter. The zone of inflammation is significantly thicker in tuberculous as compared to pyogenic abscess. The neuroimaging features of brain abscess vary with lesion stage as shown in Table 3. During the cerebritis stage (local suppurative encephalitis or immature abscess), ring enhancement may be absent or incomplete. Abscesses with a more nodular rim are often mistaken for neoplasm. Brain abscesses tend to have a smooth, thin walled capsule and it is more irregular in tumors. In contrast to tumor, the abscess rim is typically thicker near the cortex and thinnest near the ependyma. Early capsule stage is characterized by formation of a distinct collagenous capsule, which is well delineated, relatively thin, uniform and continuous. The uniformly enhancing capsule is typical of a mature abscess. The abscess gradually shrinks, peripheral edema diminishes and then disappears in the late capsule stage.

The apparent budding of smaller, “daughter” lesion from the main mass is called as “daughter abscess”. In about 50% of cases, the medial wall of an abscess is thinner than the lateral one and is thought to be due to the relatively poor vascular supply of the white matter. This explains the tendency of abscess to rupture into the ventricles and the development of secondary abscesses (daughter abscess) medially [45] may be seen near the primary lesion as in Figure 6 and Figure 7. In deep seated, multiloculated and periventricular abscesses, a reduction of 1 mm in the distance between the ventricle and brain abscess wall increases the rupture rate by 10% [46]. Smooth, <5 mm thick with medial thinning helps in differentiating an abscess from a cystic tumor and a finding of gas within

Table 3. The CT features of brain abscess according to the stages of development.

<table>
<thead>
<tr>
<th>Stages</th>
<th>CT appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early cerebritis</td>
<td>May be invisible. Poorly marginated cortical or subcortical hypodensity with mass effect with little or absence of enhancement. An ill-defined area of low density on plain CT corresponds to developing necrotic center in the cerebritis stage.</td>
</tr>
<tr>
<td>Late cerebritis</td>
<td>Irregular ring-enhancing lesion with a hypodense center, better defined than early cerebritis.</td>
</tr>
<tr>
<td>Early capsule</td>
<td>Well-defined rim-enhancing mass, an outer hypodense and inner hypodense rim (double rim sign) is seen in most cases. A slightly hyperdense, faint ring is seen surrounding a necrotic hypodense center [44].</td>
</tr>
<tr>
<td>Late capsule</td>
<td>Rim-enhancing lesion with thickened capsule and diminished hypodense central cavity. The capsule is seen as a ring in plain CT.</td>
</tr>
</tbody>
</table>
Figure 5. CT brain showing the large abscess cavity in the parietal lobe with mild midline shift in a 16-year old boy with Tetralogy of Fallot. Upper arrow showing the Rim (capsule) and the lower arrow showing the abscess cavity.

Figure 6. CT brain showing the large abscess cavity in the parietal lobe with “daughter abscess” in the lower part (lowest arrow) with moderate midline shift in a 16-year old boy with Tetralogy of Fallot.
Figure 7. CT brain showing the large abscess cavity in the parietal lobe with small “daughter abscess” in the upper part (right arrow) in a 16-year old boy with Tetralogy of Fallot.

the lesion favor a diagnosis of an abscess. Unfortunately, brain abscess may spontaneously bleed, presenting as an intracerebral hemorrhage [47].

As reported by Landriel et al. [48], brain abscesses were solitary in 77.7% of the subjects and multiple (22.3%) abscesses are more common in immunocompromised children and infective endocarditis [49]. The temporoparietal region was the most commonly affected location in a study carried out by Cavusoglu et al. [50]. In children, the most common location was in the parietal region (55%), frontal (28%), temporal (13%) and occipital (4%). The location of brain abscess as stated by Brook [51] was frontal lobe (47.1%), parietal (29.4%), temporal (13.7%) and occipital (9.8%).

MRI has also proven to detect small, multiple abscesses and may render superior images of posterior fossa location and more sensitive to distinguish cerebritis from necrosis [52], but not better than CT in distinguishing abscesses from neoplasms and the diffusion-weighted imaging can aid in this distinction [53] as hypointense abscess capsule on T2-weighted sequence may allow for this differentiation and the surrounding edema is apparent whereas in T1-weighted image, the capsule enhances and the interior of the abscess is hypointense. In T2-weighted images, the wall of the abscess is dark and it is bright in neoplasms.

MRS (Magnetic resonance spectroscopy) appears to be useful in the diagnosis of abscesses arising from anaerobic infections because these species produce lactate and acetate, which are readily apparent on MRS and rarely found within tumor tissue [54].
Practically, all abscesses > 1 cm produce positive scans. Thus, CT scan appears to be adequate in most cases of brain abscess, but in very small miliary abscesses and brain stem abscess in which MRI with specialized sequence or MRS is indicated.

**Management**

The first reference to brain abscess is attributed to Hippocrates in the fifth century B.C [55]. Sir Williams MacEwen was called as the “father” of modern brain abscess management for the publication of his famous monograph Pyogenic Infective Diseases of the Brain and Spinal cord in 1893. The treatment of brain abscess has been a challenge. The basic principle of treatment is the selection of appropriate antibiotics with or without aspiration.

**Medical Therapy**

Small brain abscesses have been treated empirically with antibiotics [56]. Heineman and colleagues became the first to report the successful medical management of a brain abscess in 1971 [57]. Medical therapy alone can be considered in patients with a lesion in the cerebritis stage since they are much more likely to respond to antibiotic therapy because of lack of a capsule [58] and also for walled off, but <2 to 3 cm in diameter abscess [59] or surgically inaccessible abscesses such as brain stem abscesses [60]. The first report of an encapsulated abscess cured by medical therapy alone was published by Chow et al. in 1975 [61]. Rosenblum, Mampalam and Pons recommended that nonoperative treatment of brain abscess should be reserved for abscess < 1.5 cm or for patients with uncontrollable bleeding diathesis.

The complexity of microbial flora in brain abscess necessitates empirical antibiotic therapy against both aerobic and anaerobic organisms. Usually, intravenous administration of “triple high dose” antibiotics (3rd generation cephalosporin + vancomycin and metronidazole) for 2 weeks followed by 4 weeks of oral therapy is recommended. The third generation cephalosporins have good central nervous system penetration and excellent in vitro activity against many pathogens isolated from bacterial brain abscess. Metronidazole is highly active against anaerobic bacteria, including *Bacteroides fragilis*, the most resistant anaerobe. Metronidazole readily penetrates brain abscess, intralesional concentration have been found to be 40 µg/ml and attains high concentration in the pus [62]. Therefore, metronidazole is usually combined with third generation cephalosporin (cefotaxime or ceftriaxone) or penicillin G for the treatment of cyanotic brain abscess [63], but is not active against aerobic organisms including microaerophilic streptococci and the duration of treatment is usually 4 - 6 weeks [64].

Sulfa drugs are most effective in Nocardia abscess and vancomycin against staphylococcus. Neurotoxicity such as seizures have been reported with imipenem [65] and meropenem should be preferred for abscess due to multidrug-resistant *Enterobacter cloacae* [66] and successful outcome has been reported. Quinolones can lower seizure thresholds [67] and should be used with caution in the treatment of cerebral abscess.

In immunocompromised patients, empirical therapy should be avoided since
they are more prone for infection with intracellular pathogens such as fungi (aspergillus) and bacteria like Nocardia or infection with human immunodeficiency virus, emphasizing the need for specific microbiological diagnosis as biopsy of the lesion may reveal a tuberculoma, which responded to antituberculous drugs [68].

**Hyperbaric Oxygen Therapy (HBO₂ or HBOT)**

It is indicated as a primary and adjunct treatment to reduce intracranial pressure and high partial pressure of oxygen act as a bactericide and thus inhibit the anaerobic flora common in brain abscess. It optimizes the immune function, enhancing the host defence mechanisms and it has been found to be of benefit when brain abscess is concomitant with cranial osteomyelitis. It also increases the stem cell production and up-regulation of VEGF which aid in the healing and recovery process [69].

**Antiinflammatory Agents**

The glial cell activation in brain abscess is through parenchymal microglia and astrocytes. Activated microglia has the potential to influence the type and extent of antibacterial adaptive immune response through upregulation of MHC class II and costimulatory molecule expression. The control release of proinflammatory mediators may damage the surrounding brain parenchyma [70] and the cytokines IL-1 and TNF-α establish an effective antibacterial response in the CNS parenchyma. Recent studies support persistent immune activation in brain abscess with elevated levels of IL-1, TNF-α and macrophage inflammatory protein-2 (MIP-2), detected 14 to 21 days following staphylococcus aureus exposure.

Interventions with anti-inflammatory agents subsequent to sufficient bacterial neutralization may be an effective strategy to minimize the damage in the surrounding brain parenchyma during the course of brain abscess development, leading to improvements in cognition and neurological outcome [71].

However, if coagulation abnormalities are present, especially in cyanotic CHD, nonsteroidal anti-inflammatory drugs should be avoided, platelet concentrate needs to be available perioperatively [72] and when the hematocrit > 65% requires phlebotomy and adequate hydration to maintain intravascular volume.

**Role of Steroids**

Corticosteroids play a role as an adjunctive therapy to control cerebral edema in patients with potentially life-threatening complications such as impending cerebral herniation. Corticosteroids are used when a significant mass effect is visible on imaging and the patient’s mental status is depressed, but had some adverse effects to retard the encapsulation process [73] [74], increase necrosis, reduce antibiotic penetration (polar antibiotics such as benzylpenicillin) into the abscess, increase the risk of ventricular rupture, and decrease the enhancement of abscess wall on CT due to contrast reduction as inflammation subsides [75]. The tissue concentrations of more lipophilic substances, such as metronidazole, were not affected by concomitant corticosteroid therapy [76] and it should be the part of antibiotic regimen. The corticosteroid of choice for reducing the in-
tracranial pressure is dexamethasone and it may decrease inflammation by suppressing the migration of polymorphonuclear leukocytes and reversing increased capillary permeability. When used to reduce the cerebral edema, therapy should be of short duration and high-dose corticosteroid therapy (IV dexamethasone 8 mg every 8 hours) should be given and then tapered off after the patient’s condition has stabilized. Even though retrospective studies failed to show a beneficial effect of corticosteroids on outcome [77] [78], however, corticosteroids are given mostly to severely obtunded and comatose patients who are known to have a dismal prognosis [79] [80]. Severe brain abscess may necessitate further measures to reduce the increased intracranial pressure, such as osmotherapy (e.g. mannitol) and hyperventilation. Even though mannitol helps to decrease intracranial pressure, cerebral edema and ideal to reduce blood viscosity, it can cause severe dehydration, hypotension, tachycardia, acidosis and precipitate “tet spell”.

**Surgical Therapy**

Surgery is the treatment of choice for most brain abscess to confirm the diagnosis, allow direct identification of the causative organism, and to decompress the abscess cavity. A number of surgical techniques have been developed to treat brain abscess over the last two centuries, range from the tube drainage methods of the past to modern computer-guided minimally invasive approaches for abscesses < 1.5 cm accurately with minimal morbidity. The first successful operation for brain abscess was performed by French surgeon S. F. Morand in 1752 on a temporoethmoidal abscess [81]. King introduced marsupialization in 1924 [82] and Dandy introduced aspiration in 1926 [83]. Sargeant considered the procedure of enucleation of an encapsulated brain abscess in 1928 [84] and Vincent popularized complete excision and proved its value in 1936.

Surgical drainage provides the most optimal therapy and the procedures used are aspiration through a burr-hole and complete excision after craniotomy. Needle aspiration is preferred and the most commonly used technique, often performed using a stereotactic procedure with a guidance of ultrasound or CT scanning [85], especially for deep-seated abscesses (brainstem, cerebellum and basal ganglia). Often, external drainage of the abscess through an intra-cavity catheter is recommended for abscesses > 3 cm in diameter. Total excision is preferred for solitary, superficial and encapsulated abscesses. Abscess containing gas are resistant to antibiotics and are better treated with excision [86]. Brain abscess caused by *Nocardia asteroides* are multiloculated and excision must be performed to effect a cure [87] and may not be successfully treated by aspiration. Excision is also reserved for abscesses that enlarge after 2 weeks of antibiotic therapy or that fail to shrink after 3 - 4 weeks of antibiotics because of adhesions to the dura and also for posterior fossa abscesses, especially in the cerebellum, which may compress CSF pathways and thereby lead to dangerously high intracranial pressure and carry a mortality rate of 20% to 50% [88]. The current recommendations are to drain these abscesses through a posterior fossa craniotomy and to perform CSF diversion through an external ventricular drain in patients with any radiologic signs of hydrocephalus. Excision should not be considered for abscesses in
the cerebritis stage, deep-seated abscesses in the eloquent areas and multiple abscesses.

The “migration technique” described by Khan in 1937 [89] is a two-stage technique that included a decompressive craniotomy followed by a second procedure 3 to 4 days later for either excision or drainage of the abscess. He noted when a craniotomy was performed for the relief of increased intracranial pressure, brain abscess tended to migrate toward the cranial opening.

Neuroendoscopic technique with freehand stereotaxy has also been practiced [90] and it has an additional advantage of more complete drainage and lavage, when compared to stereotactic aspiration [91].

It is suggested that irrigation of abscess cavity with antibiotic solution raises antibiotic levels and reduces the bacterial load, allowing the infectious process to resolve more quickly [92]. However, local administration of antibiotics is not routinely recommended because intravenous antibiotics used for brain abscess treatment penetrate the brain and abscess capsule, achieving therapeutic intracavitary levels [93]. Antibiotic irrigation may prove helpful in case of rupture of a brain abscess into the ventricle [94].

**Five Component Therapy**

The encapsulation of a brain abscess often is more complete on the cortical than on the ventricular side. Thus, it is more likely to rupture into the ventricles rather than laterally into the subarachnoid space. The intraventricular rupture of brain abscess (IVOBRA) results in severe headache, an increase of meningeal irritation, a rapidly deteriorating clinical condition, and an enhancement of the ventricular wall adjacent to the abscess often preceded IVOBRA [95]. Most authors proposed an aggressive approach with regard to its clinical prognosis. Zeidman, Geisler, and Olivi have proposed a five-component therapeutic plan [96], consisting of open craniotomy with debridement of the abscess cavity, lavage of the ventricular system, ventricular drainage, intrathecal gentamycin, and intravenous administration of appropriate antibiotics. However, the role of intrathecal antibiotics is disputed [97].

Seizure is a long term risk for up to 30% - 50% of patients suffering from brain abscess [98]. The hypo-dense areas surrounding the abscess cavity are thought to cause epileptic activity and it is mainly related to scars after excision rather than with aspiration. Antiepileptic medication was advised in all cases and continued for at least 2 years and then slowly withdrawn when the EEG remains normal and the patient is seizure free for at least 2 years after surgery. Legg advocated anticonvulsant therapy for 5 years to all patients with cerebral abscess [99]. Seizures are initial presentation of brain abscess up to 35% of cases and should be controlled with intravenous benzodiazepines such as lorazepam or midazolam or fosphenytoin. For the prevention of further seizures, carbamazepine is recommended, in addition to phenytoin.

The risk of recurrence is 10% - 50%. To prevent recurrence of the abscess, the source of infection should be treated surgically or medically [100]. Correction of
cardiac anomaly is necessary to prevent recurrent brain abscess in cyanotic CHD.

**Case Analysis**

The primary source of infection in this case is vegetative lesion in the heart, which in turn leads to hematogenous dissemination to brain, resulting in abscess formation, when the filtering effect of lungs, the current theory of mechanism, is circumvented in Tetralogy of Fallot and the abscess is usually solitary in children. The boy was afebrile since the fever is characteristic of early invasive phase of cerebritis and may return to normal similarly with leukocytosis when the abscess was encapsulated. The size of an abscess may not change for >2 weeks after the institution of successful medical therapy [101] and it may needs 10 weeks before the abscess resolved on CT scanning. The ineffectiveness of antibiotics in the stage of capsule formation is due to the acidic medium within the abscess cavity and the inability to have adequate therapeutic concentration of antibiotics within the abscess. Therefore, surgical treatment is essential once the abscess is encapsulated [102]. Stereotactic aspiration is appropriate for abscesses located in the eloquent regions of the brain because it provides a direct and rapid access to the abscess through a predetermined route. Penetration of a thick abscess wall with a blunt-tipped stereotactic probe can be difficult and so freehand aspiration technique was preferred in this case.

**Outcome**

Long term outcome in children included complete recovery (30%), hemiparesis (37%) and seizure disorder (16%) [103]. According to four recent studies, the mortality rate of brain abscess was 13% (6% - 24%) [104], which had decreased substantially after the introduction of CT scanning.

**4. Conclusion**

Brain abscess associated with cyanotic CHD, when presented with rapidly progressive neurological deficit due to mass effect is an indication for urgent decompression. The resolution of surrounding edema and enhancing rim may take up to 6 months and the abnormal enhancement on CT can persists for years after the successful treatment of abscess due to mild breakdown of blood-brain barrier, but not due to residual infection [105] [106].

**Conflicts of Interest**

The author declares no conflicts of interest regarding the publication of this paper.

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Posterior Reversible Encephalopathy Syndrome Induced by Pazopanib in a Patient with Soft-Tissue Sarcoma: A Case Report

Chien-Ting Wu, Chieh-Tsung Yen, Hsiu-Lan Cheng, Chi-Hui Lee
Department of Pharmacy, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taiwan
Email: xelox78123@gmail.com

Abstract
Posterior reversible encephalopathy syndrome (PRES), a rare disease is characterized by multiple neurological complications. It has been reported to be associated with the use of angiogenesis inhibitors such as sorafenib, sunitinib, pazopanib, regorafenib, and lenvatinib. We reported a case of 76-year-old woman with history of stage III hepatocellular carcinoma (HCC), who developed adverse drug reactions related to pazopanib induced PRES. Pazopanib, an angiogenesis inhibitor which inhibits the vascular endothelial growth factor (VEGF) pathway may lead to vascular endothelial damage, and these pathophysiological changes may lead to vascular leaks and brain edema. Medical staff must be aware of the possible association between angiogenesis inhibitors and the development of PRES. In patients with retroperitoneal soft-tissue sarcoma undergoing treatment with pazopanib, regular monitoring of their blood pressure and following-up brain magnetic resonance imaging (MRI) should be encouraged.

Keywords
Posterior Reversible Encephalopathy Syndrome, Pazopanib, Hepatocellular Carcinoma, Vascular Endothelial Growth Factor, Magnetic Resonance Imaging

1. Introduction
Posterior reversible encephalopathy syndrome (PRES) is a rare disease, which is characterized by multiple neurological complications [1] such as seizures and hypertensive emergencies [1] [2]. Commonly clinical manifestations of PRES include severe headache, confusion, seizures and visual disturbances, as
well as signs of symmetrical white matter edema [3] under brain magnetic resonance imaging (MRI) study [1]. In the last few years an increased number of case reports involving new targeted drugs, particularly angiogenesis inhibitors such as sorafenib, sunitinib, pazopanib [4], regorafenib [5], lenvatinib [6] and other targeted drugs have been implicated in new cases of PRES [3]. This case represented a patient with hepatocellular carcinoma (HCC) under pazopanib using that developed multiple clinical adverse reactions including signal change under MR image study, which elicits highly suspicious of pazopanib induced PRES.

2. Case Presentation

We present the case of a 76-year-old woman, who has history of stage III hepatocellular carcinoma (HCC), and ureter tumor s/p left nephrectomy and ureterectomy. She also has underlying medical illness such as diabetes and end stage renal disease under regular hemodialysis three times a week in the San Joseph’s Hospital. Her HCC and bladder tumor was under regular medical follow-up in the Chia Yi Christian hospital. The HCC was under medication controlled with pazopanib 400 mg BID PO since Oct. 26, 2017, and combined with oral drugs at home since Oct. 7, 2017 (shown in Table 1). At 7 o’clock on Oct. 29, the patient was found having four limbs generalized myoclonic movement accompanied with upward gazing with the duration persisted for about 5 minutes at home, and she was then brought to our hospital for medical attention. Her consciousness became drowsy after arrival of the paramedical and similar episode attacked again in the ambulance. She never has any previous history of seizure attack neither fever, chills nor headache. At the ER, her vital signs (T/P/R) were 36.6/98/19 and the NBP was 93/77 mmHg, the neurologic examination demonstrated isocoric pupils with size about 2.5 mm, both reactive to the light, and the muscle power of four limbs were three fractions. Under the impression of myoclonic seizure, 2 mg lorazepam was stat given with intravenous drip, 1000 mg levetiracetam was loading intravenously, and CNS dose ceftriaxone was administrated, and she was admitted into the medical intensive care unit for close monitoring. The MRI obtained on Oct. 30, 2017 revealed multiple high signal change with edematous areas over subcortical region of frontoparietal lobe, periventricular region, occipital lobe, splenium, and hemisphere of cerebellum (Figure 1). Owing to the symptoms associated with acute changes in consciousness and seizures, along with exacerbated systemic hypertension (shown in Table 2), PRES associated with the use of pazopanib was highly suspected, and pazopanib was discontinued on Oct. 11, 2017. Under the impression of PRES with associated clinical symptoms, she was treated with the anti-convulsant (levetiracetam 500 mg TID PO and clonazepam 0.5 mg HS PO) continuously for more than 1 month, and simultaneously anti-hypertensive drugs were administrated (continuously intravenous infusion of nicardipine for two days, followed by intravenous labetalol, and then switch to amlodipine orally) for keeping systolic blood pressure.
Figure 1. Brain MR images revealed hyper-intense signals over subcortical region of bilateral frontoparietal lobe and periventricular area (top 2 figure), splenium (mid. left), and bilateral occipital lobes (mid. right), right lateral-temporal lobe (bottom left), and dorsal pons, as well as bilateral hemisphere of cerebellum (bottom right) in the patient with PRES.

Table 1. Daily oral drugs before PRES presentation with the patient.

<table>
<thead>
<tr>
<th>Name of Drugs</th>
<th>Dosage</th>
<th>Frequent</th>
<th>Oral Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pazopanib</td>
<td>400 mg</td>
<td>BID</td>
<td>PO</td>
</tr>
<tr>
<td>Thiamine &amp; Riboflavin</td>
<td>50 &amp; 5 mg</td>
<td>QD</td>
<td>PO</td>
</tr>
<tr>
<td>Folic Acid</td>
<td>5 mg</td>
<td>QD</td>
<td>PO</td>
</tr>
<tr>
<td>Famotidine</td>
<td>20 mg</td>
<td>BID</td>
<td>PO</td>
</tr>
<tr>
<td>Calcitriol</td>
<td>0.75 mcg</td>
<td>QW135</td>
<td>PO</td>
</tr>
<tr>
<td>Cortisone</td>
<td>25 mg</td>
<td>QD</td>
<td>PO</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0.25 mg</td>
<td>TID</td>
<td>PO</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0.5 mg</td>
<td>HS</td>
<td>PO</td>
</tr>
</tbody>
</table>
around 100 to 130 mmHg. Her symptoms were gradually improved on the fifth hospital day. Due to advanced blood pressure control, she completely regained consciousness with gradually symptom improved on the fifth hospital day, and there was no subsequently new onset neurologic deficits nor clinical seizure attack on the following days, and she was discharged on Oct. 27, 2017. The anti-epileptic drugs such as levetiracetam and clonazepam were continued for symptoms control after discharge.

3. Discussion

After reviewing medication profile and further analyzing with reference of relevant literatures, we suspected PRES associated with the use of pazopanib. PRES, which can be fatal, was reported in patients who received pazopanib. Pazopanib should be permanently discontinued if patients associated with the development of PRES [7]. Pazopanib is an oral tyrosine kinase inhibitor (TKIs) that blocking vascular endothelial growth factor (VEGF), platelet-derived growth factor receptor and c-Kit signaling to inhibit the proliferation of tumor cells, and is ap-

Table 2. Daily vital sign in the patient with PRES within the seventh hospital day.

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
<th>Temperature (°C)</th>
<th>Pulse Rate (min)</th>
<th>Respiratory Rate (min)</th>
<th>Blood Pressure (mmHg)</th>
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<tr>
<td>10/29</td>
<td>1100</td>
<td>36.5</td>
<td>98</td>
<td>21</td>
<td>175/89</td>
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<td></td>
<td>1600</td>
<td>36.5</td>
<td>100</td>
<td>22</td>
<td>191/100</td>
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<tr>
<td></td>
<td>2100</td>
<td>37.2</td>
<td>92</td>
<td>20</td>
<td>189/96</td>
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<tr>
<td>10/30</td>
<td>900</td>
<td>36.5</td>
<td>80</td>
<td>20</td>
<td>166/85</td>
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<tr>
<td></td>
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<td>35.7</td>
<td>79</td>
<td>18</td>
<td>109/61</td>
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<tr>
<td>10/31</td>
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<td>36.5</td>
<td>90</td>
<td>16</td>
<td>150/67</td>
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<td>36.6</td>
<td>76</td>
<td>16</td>
<td>135/69</td>
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<td>88</td>
<td>15</td>
<td>160/71</td>
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<td>11/2</td>
<td>900</td>
<td>36.7</td>
<td>81</td>
<td>20</td>
<td>116/67</td>
</tr>
<tr>
<td></td>
<td>1300</td>
<td>36.4</td>
<td>79</td>
<td>18</td>
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<td>36.8</td>
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<td>72</td>
<td>18</td>
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<td>900</td>
<td>37.1</td>
<td>77</td>
<td>18</td>
<td>109/64</td>
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<tr>
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<td>73</td>
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<td>20</td>
<td>138/66</td>
</tr>
</tbody>
</table>
proved for use in advanced renal cell carcinoma and soft-tissue sarcoma, currently [2] [8]. Pazopanib significantly improved the progression-free survival (PFS) of patients with soft tissue sarcoma, but 41% of patients will cause hypertension, acute and severe hypertension may cause vasodilation and imbalance of brain auto regulation (disruption of cerebral autoregulation), which causes a breakdown of the blood-brain barrier [1]. In Neurologic effects, 10% of patients cause headaches, confusion, seizures, and visual impairment. Inhibition of the VEGF pathway may lead to vascular endothelial damage, and these pathophysiological changes may lead to vascular leaks and brain edema, which seriously causes PRES [1]. The hallmark of PRES in the majority of the cases of clinical symptoms and brain imaging findings, usually occurs within days to weeks. The major adverse events include: malignant hypertension, preeclampsia, eclampsia and some post-transplant drug treatments (tacrolimus and cyclosporine) or autoimmune disease [3]. In a typical case, angiogenic edema in the apical and posterior frontal lobes is usually seen on the neuroimaging [1] [3]. On vascular images, there are often diffuse vasoconstriction, irregular or partial vasoconstriction of blood vessels, and vasodilation [2] [9]. In a randomized, double-blinded, controlled study of soft tissue sarcoma treatment, the results found that approximately 42% of patients with soft tissue sarcoma who received pazopanib associated with the development of hypertension (systolic blood pressure > 150 or diastolic blood pressure ≥ 100 mmHg) and hypertensive crisis. Hypertension occurs early in the course of treatment (40% of cases occurred before the 9th day, 90%) [10]. The case occurred within the first 18 weeks), so blood pressure should be monitored early after starting treatment (not more than one week), 4% to 7% of patients receiving pazopanib which have grade 3 hypertension; approximately 1% of patients who received pazopanib permanently discontinued treatment due to hypertension [10]. In the literature, an initial goal of blood pressure reduction not more than 25% within several hours of the onset of PRES using continuous intravenous administration of anti-hypertensive agents was recommended [11]. PRES should be considered as the actual reason for neurologic findings in hypertensive patients with metastatic cancers under TKI therapy. As with other conditions, fluctuations of blood pressure should be avoided and the continuous administration of antihypertensive drugs should be considered under hemodynamic monitoring [12]. In our case, we have been closely monitoring her blood pressure during hospitalization for this patient with end stage renal disease under regular hemodialysis.

4. Conclusion

According to the Naranjo algorithm, the PRES was probably related to pazopanib usage, we concluded that pazopanib has probably caused the adverse reactions (Naranjo Algorithm Score of 5) in this patient (shown in Table 3). Medical staff must be aware of the possible association between angiogenic inhibitors therapy and the development of PRES. In patients undergoing treatment with
Table 3. Naranjo algorithm.

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Do Not Know</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Are there previous conclusive reports on this reaction?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2) Did the adverse event appear after the suspected drug was administered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3) Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4) Did the adverse event reappear when the drug was re-administered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5) Are there alternative causes (other than the drug) that could on their own have caused the reaction?</td>
<td>-1</td>
<td>+2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6) Did the reaction reappear when a placebo was given?</td>
<td>-1</td>
<td>+1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>7) Was the drug detected in blood (or other fluids) in concentrations known to be toxic?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>8) Was the reaction more severe when the dose was increased or less severe when the dose was decreased?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>9) Did the patient have a similar reaction to the same or similar drugs in any previous exposure?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>10) Was the adverse event confirmed by any objective evidence?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

pazopanib, regular monitoring of their blood pressure and follow-up with brain MRI should be encouraged.

Acknowledgements
None.

Conflicts of Interest
None to declare. Each author certifies that he or she has no financial organization (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article. There are no other conflicts of interest. The case described in the article was performed with funding from Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chia-Yi, Taiwan.

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Sinonasal Squamous Papilloma with Orbital Infiltration in an Elderly Nigerian Female, Unusual Presentation of an Uncommon Tumor: A Case Report

Oyeleye A. Oyelakin¹, Oluymemi Fasina²*, Clement A. Okolo³, Funsho J. Akande¹, Onyekwere G. Nworgu¹,⁴

¹Department of Otorhinolaryngology, University College Hospital, Ibadan, Nigeria
²Department of Ophthalmology, University College Hospital, University of Ibadan, Ibadan, Nigeria
³Department of Pathology, University College Hospital, University of Ibadan, Ibadan, Nigeria
⁴Department of Otorhinolaryngology, University of Ibadan, Ibadan Nigeria

Email: *yemifash2000@yahoo.com

Abstract

Squamous papillomas are squamous-derived growths commonly arising from the oral cavity and oropharynx. A 75-year-old woman presented with chronic persistent left nasal obstruction and gradual painless non-axial proptosis with loss of vision in the left eye. Computed tomography scan showed an iso-dense lesion filling the frontal, left ethmoidal and sphenoid sinuses, and the nasal cavity, with extension into the left orbit. She underwent surgical tumor resection with orbital exenteration and histology revealed features of an aggressive hyperkeratotic squamous papilloma arising from the sino-nasal region. Although squamous papillomas have been natively associated with the oral cavity and oropharynx, they present less frequently as sino-nasal tumors with orbital invasion.

Keywords

Orbital Tumor, Sino-Nasal Tumor, Proptosis Squamous Papilloma

1. Introduction

Papillomas are benign tumours with characteristic papillary projections and are among the most common benign epithelial tumours of the oral cavity in both children and adults, but most commonly seen in persons between 30 and 50 years of age [1]. Squamous papillomas are common, squamous-derived growths
of the oral cavity and oropharynx typically presenting as a single, asymptomatic, soft, pedunculated mass with numerous finger-like projections at the surface [2] [3]. In the head and neck region, occurrence of this lesion is relatively rare in the paranasal sinuses whereas oral squamous papilloma is the fourth most common mucosal mass in humans accounting for 3% - 4% of all biopsied lesions [4].

To the best knowledge of the authors, orbital involvement of this tumor has not been reported in Nigeria; hence, this reports the presentation and management of sino-nasal squamous papilloma with orbital involvement in an elderly Nigerian female.

This study adhered to the Tenets of Declaration of Helsinki and an informed consent was obtained from the patient for the publication of the report.

2. Case History

A 75-year-old lady presented with persistent left nasal obstruction of 2 years, and gradual painless protrusion with loss of vision in the left eye of about 6 months duration. There was associated ipsilateral purulent nasal discharge and loss of smell but no history of persistent sneezing, itching, or nosebleed. The right nasal cavity and right eye were symptom-free.

At presentation, the ear, oral cavity, neck, and oropharyngeal examinations were essentially normal. However, there was a pink firm mass in the left nasal cavity with greenish-yellow discharge, no distortion of the nasal pyramid and the airflow was completely obstructed. There was left non-axial proptosis of 12 mm with inferotemporal globe displacement, conjunctival chemosis, keratinized and opacified cornea, and nil detailed view of intraocular structures. The orbit was filled with a firm soft tissue tumour and visual acuity was nil perception of light. The right ocular examination was essentially normal as she had only early lenticular opacity which was compatible with her age.

Computed tomography scan showed an iso-dense lesion filling the frontal, left ethmoidal and sphenoidal sinuses, nasal cavity and extending into the left orbit (Figure 1). Hematological profile of the patient was essentially normal.

She was reviewed by both the ophthalmologist and otorhinolaryngologist and subsequently underwent left lid-sparing orbital exenteration, with sino-nasal tumour excision via a transorbital ethmoidectomy and trans-nasal approach. She also had inferior meatal antrostomy which revealed minimal aspirates but no mass was in the maxillary cavities. The sino-nasal tumor mass appears fleshy, polypoid and pale on gross examination. She had intranasal packing with Bismuth Iodoform Paraffin Paste intra-operatively, and immediate post-operative recovery was satisfactory.

Histopathological sections of the extra-ocular tumour showed a benign epithelial neoplasm composed of multiple complex exophytic papillomatous fronds having prominent fibrovascular cone and lined by keratinizing squamous epithelial cells with occasional columnar and mucous containing cells. The basal layer showed occasional mitosis with mild atypia of the lining cells and growth of this tumor stopped short of the globe (Figure 2). Sections of the globe showed
Figure 1. Computed tomography scan showing an iso-dense lesion filling the frontal, left ethmoidal and sphenoidal sinuses, nasal cavity and extending into the left orbit.

Figure 2. Photomicrograph of the squamous papilloma showing the tumor composed of multiple polypoid fronds of tissue lined by squamous epithelial cells showing mild to moderate cytonuclei-pleomorphism and loss of polarity.

only a fragment of atrophic optic nerve possibly due to compression by the tumour while the globe showed no remarkable features. Overall features were suggestive of an aggressive hyperkeratotic squamous papilloma arising from the sino-nasal region. She fared well post-operatively, and has been followed up for about six months with no recurrence of tumor.

3. Discussion

Sino-nasal tumours which extend into the orbits usually arise from the maxilla-ethmoid complex [5], however, the index case had orbital tumor invasion from the superior-medial wall. Orbital invasion from sino-nasal tumors can occur via various anatomic paths and Saha et al. [6] in their study, reported that
inverted papillomas invaded the orbit via the sphenoid in 4% of cases, and via erosion of the lamina papyracea in 13% of cases. Orbital tumors cause proptosis, the anterior protrusion of the eyeball within the orbit and this can be from primary space occupying lesions of the orbit, secondary extension from the para-orbital structures, or distant metastasis. Keche et al. [5] in their review of causes of unilateral proptosis reported that 85% of unilateral proptosis resulted from para-orbital tumors, 10% were primary orbital tumors, and 5% from distant metastasis. Similarly, our patient had unilateral proptosis following orbital tumor invasion from a primary sino-nasal tumor.

Squamous papilloma is benign tumor in the spectrum of papillary tumors affecting the oral cavity [7] and there is a strong association between Human Papilloma Virus and the tumor [1]. The history of progressive nasal obstruction is common to both benign and malignant nasal growths, but nasal obstruction of long duration as reported in this elderly woman is suggestive of a benign pathology [6]. Typically, the involvement of the orbit in sino-nasal tumors is seen in paraorbital malignant conditions [5], however, when associated with benign conditions, the common pathologies include inverted papilloma, juvenile angiofibroma, fungal sinusitis and other infectious conditions [8] [9] [10] [11].

The differential of the clinical presentation of a yellowish-green nasal discharge and gradual painless proptosis include chronic sino-nasal fungal infection [12] [13]. Although, mycology studies were not carried out on the excised tissue, the histopathological examination did not show typical features suggestive of fungal disease such as the presence of granulomas with refractile fungal hyphae and spores. Epistaxis, facial deformity, diplopia, facial numbness and other features suggestive of malignant sino-nasal tumours [14] were also absent in our patient.

Visual affection is uncommon in benign orbital conditions [5], however, the long-standing orbital infiltration with severe proptosis, and possibly, compressive optic neuropathy could account for the loss of vision in this elderly woman.

Appropriate imaging is complementary to symptomatology in making a presumptive diagnosis of sino-nasal tumours, however, they are not substitutes to histological diagnosis [15]. Imaging also aids in the determination of tumour margins and attachment sites, and a combination of computed tomography (CT) scan, magnetic resonance imaging (MRI) and positron emission tomography. (PET/CT), could be carried out [16]. The CT scan of the paranasal sinuses and orbits, which is the most preferred radiological imaging, was carried out in the patient. This showed tumor involvement of the paranasal sinuses and orbit, and also, an iso-dense lesion in the left maxillary sinus, which intraoperatively was found to be impeded secretions caused by blockage of the osteo-meatal complex by the tumour.

Definitive treatment of squamous papilloma is basically total surgical excision [3]. Sino-nasal tumors could be removed via endoscopic sinus surgery, by external surgical approach, or a combination of the two [17]. Excision of the tumor by ethmoidectomy via the orbital cavity was appropriate in this case following
orbital exenteration. The portion of the tumour in the left nasal cavity was easily accessed through the trans-nasal approach with a pair of Luc’s forceps.

4. Conclusion

In conclusion, although squamous papillomas have been natively associated with the oral cavity and oropharynx, they can present as sino-nasal tumors with orbital invasion. Surgical excision is the mainstay of management of squamous papilloma and histological differentiation from malignant conditions like verrucous carcinoma which is very important to guide the post-operative treatment.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References


Resident Hospital Discharges by Severity of Illness at the Regional Level

Ronald Lagoe*, Gretchen Lagoe

Hospital Executive Council, Syracuse, NY, USA
Email: *Hospexcl@cnymail.com

Abstract

In the twentieth century, government sponsored health planning focused on the use of services by population in the United States. This case study evaluated the impact of severity of illness for resident hospital discharges for 2017, the latest time period for which this information was available. It focused on the Central New York Health Service Area, one of the original health planning populations. The study demonstrated that patients at Extreme severity of illness constituted similar percentages of adult medicine and adult surgery populations in the Central New York Region. The sizes of Moderate severity of illness populations were also similar. The study identified considerable differences in the sizes of Minor and Major severity of illness populations for adult medicine and adult surgery in the Central New York Region. These differences resulted from large numbers of healthy patients in the adult surgery population. They were admitted for orthopedic procedures and procedures to address obesity.

Keywords

Hospitalization, Hospital Discharges, Severity of Illness

1. Introduction

In the United States and elsewhere, health care is closely associated with community and regional populations. The need for these services is generated by resident populations [1] [2].

Historically, health planning has focused on the utilization of services at regional and community levels. These initiatives have included the Health Systems Agencies developed by the federal government in the twentieth century, as well as State and local efforts to evaluate and regulate providers [3] [4].

These health planning programs focused on generating voluntary compliance
from providers. Some of them were linked with payor approvals for specific projects, such as the Certificate of Need programs. They were administered by state or local planning staffs [3].

Most of these health planning programs were implemented before the use of current approaches to health care reimbursement and evaluation. They frequently employed relatively simple analytical tools, such as resource to population ratios.

Many of these programs phased out before the advent of more sophisticated approaches to hospital management. Reimbursement by discharge employing Diagnosis Related Groups was first implemented by Medicare in 1983. The evaluation of inpatient utilization by severity of illness began in the 1990s [5] [6] [7].

In the twenty first century, much of the attention concerning the use of health care has focused on provider utilization. Only recently interest in the connection between utilization and demographics has been renewed in population health [8] [9].

2. Population

This case study evaluated inpatient hospital utilization with respect to discharges and severity of illness in the Central New York Health Service Area. This region is one of the original health planning areas established by the federal health planning legislation of 1976. It includes eleven counties and a population of 1,124,173 [10].

The Central New York Health Service Area is based on three groups of counties. The largest includes Onondaga County, where the City of Syracuse, the largest metropolitan area in the region, is located. Its demographics also include the Counties contiguous to Onondaga, Cayuga, Cortland, Madison, and Oswego Counties. They are populated by the suburbs of Syracuse, as well as numerous small towns and rural areas. Tompkins County, which includes the City of Ithaca, is located in the southern part of this area. Together, these six counties include a population of approximately 698,830, or 62.1 percent of the regional total.

The northern part of the Central New York Health Service Area comprises Jefferson, St. Lawrence, and Lewis Counties. Jefferson County includes the City of Watertown, a number of small towns and rural areas, and the Fort Drum Army base. St. Lawrence and Lewis Counties include a number of small towns and rural areas. These three counties include a population of approximately 194,540 or 17.3 percent of the regional total.

The eastern part of the Central New York Health Service Area comprises Oneida and Herkimer Counties. Oneida County includes the City of Utica, the second largest metropolitan area in the region, the City of Rose, as well as numerous small towns and rural areas. Herkimer County includes small towns and rural areas. These two counties include a population of approximately 231,617, or 20.6 percent of the regional total.
Regional planning in the region was the responsibility of the Central New York Health Systems Agency under federal health planning legislation during the 1970s. After the expiration of federal health planning legislation, the Central New York Health Systems Area was supported by New York State funding for approximately 20 years.

3. Method

This case study evaluated hospital discharges by All Patients Refined Diagnosis Related Groups and severity of illness in the Central New York Health Service Area during 2017, the most recent time period for which complete data were available. The study was based on adult medicine and adult surgery, the inpatient services with the largest inpatient volumes. It was based on discharges for all payors.

The study was based on these hospital services as defined by the All Patients Refined Diagnosis Related Groups developed by 3M™ Health Information Systems. It was also based on the All Patients Refined Severity of Illness System. This algorithm identifies severity of illness for each hospital inpatient based on the principal diagnosis, all secondary diagnoses, and demographic indicators such as age and gender [3].

Data for the study were obtained from the New York State Planning and Research Cooperative System. These data include all discharges from New York State hospitals for residents of the State. They do not include discharges from hospitals outside the State.

The study was conducted by the Hospital Executive Council, the planning organization for the Syracuse hospitals. The Council is responsible for studies and programs that improve efficiency in the service area of the hospitals [11].

The study focused on identification of numbers of discharges and discharges by Resident County for the eleven counties in the Central New York Health Service Area. It was based on discharges for these resident populations, regardless of provider in New York State, rather than on hospital specific utilization.

Within adult medicine and adult surgery, the analysis focused on comparison of resident county populations for patients with Minor, Moderate, Major, and Extreme severity of illness. These comparisons were made with respect to numbers of discharges and percent of total discharges for each resident county.

The study also included comparison of the distribution of hospital inpatients by severity of illness between adult medicine and adult surgery. As in the analysis for individual services, percentages of total discharges were used to standardize the distributions of inpatients by severity of illness.

4. Results

The initial component of the case study evaluated resident adult medicine hospital discharges in the Central New York Health Service Area by severity of illness. Relevant data are summarized in Table 1.
Table 1. Inpatient adult medicine discharges by severity of illness, Central New York Counties, 2017.

<table>
<thead>
<tr>
<th>Resident County</th>
<th>Number of Discharges</th>
<th>Percent of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minor</td>
<td>Moderate</td>
</tr>
<tr>
<td>Onondaga County</td>
<td>3171</td>
<td>9306</td>
</tr>
<tr>
<td>Cayuga County</td>
<td>484</td>
<td>1653</td>
</tr>
<tr>
<td>Cortland County</td>
<td>338</td>
<td>956</td>
</tr>
<tr>
<td>Madison County</td>
<td>392</td>
<td>1217</td>
</tr>
<tr>
<td>Oswego County</td>
<td>707</td>
<td>2247</td>
</tr>
<tr>
<td>Tompkins County</td>
<td>321</td>
<td>1074</td>
</tr>
<tr>
<td>Oneida County</td>
<td>2183</td>
<td>6265</td>
</tr>
<tr>
<td>Herkimer County</td>
<td>615</td>
<td>1665</td>
</tr>
<tr>
<td>Jefferson County</td>
<td>730</td>
<td>2136</td>
</tr>
<tr>
<td>Lewis County</td>
<td>196</td>
<td>606</td>
</tr>
<tr>
<td>St. Lawrence County</td>
<td>920</td>
<td>2385</td>
</tr>
<tr>
<td>Total</td>
<td>10,057</td>
<td>29,510</td>
</tr>
</tbody>
</table>

Includes patients aged 18 years and over assigned to medical APR Diagnosis Related Groups excluding obstetrics (APR DRGs 540 - 566), mental health/substance abuse treatment (APR DRGs 740 - 776), and rehabilitation (APR DRG 860). Sources: New York Statewide Planning & Research Cooperative System (SPARCS) data.

These data were identified by Resident County, rather than hospital specific discharges, within the Region. They were based on total numbers of resident hospital discharges for all payors and resident populations. They were developed for Minor, Moderate, Major, and Extreme severity of illness.

This information identified large differences in numbers of resident inpatient discharges among the Central New York Counties in 2017. The two metropolitan areas, Onondaga and Oneida Counties, generated the largest numbers of discharges. Largely rural counties such as Cortland, Madison, and Lewis produced considerably smaller numbers.

In contrast, the data indicated that variation among percentages of adult medicine patients within each of the four severity of illness categories among counties in the Central New York Health Service Area was relatively limited. The largest proportions were generated by Major severity, ranging from 32 to 43 percent and Moderate severity, from 35 to 46 percent.

The lowest and highest levels of severity accounted for much smaller proportions of total discharges among Central New York counties. Patients at Minor severity of illness accounted for 10 - 16 percent and those at Extreme severity were responsible for 6 - 13 percent. These data suggested that for adult medicine discharges, outlier patients with low and high severity were a small minority of the total resident population.

The study also included a review of resident hospital lengths of stay by severity of illness for each of the eleven counties in the region. For ten of the eleven counties, the lengths of stay increased for each severity of illness category compared with the one before.
The second component of the case study evaluated resident adult surgery discharges in the Central New York Health Service Area by severity of illness. Relevant data are summarized in Table 2.

As in the case of adult medicine, these data identified substantial differences in numbers of resident discharges among Central New York Counties in 2017. The largest numbers were generated by Onondaga County, including Syracuse, and Oneida County, including Utica. The smallest numbers of discharges were produced by largely rural counties such as Cortland and Lewis.

The data indicated that variations in percentages of total discharges for individual levels of severity among Central New York counties were limited. The largest percentages among the counties were produced by Moderate severity, 35 - 42 percent of the total, and Minor severity, 31 - 41 percent. Smaller percentages were produced by Major severity, 15 - 18 percent, and Extreme severity, 5 - 10 percent.

In comparison with the severity of illness data for adult medicine, the adult surgery data included a substantial increase for Minor severity of illness patients in the Central New York Health Service Area. Patients in this category accounted for 31 - 41 percent of the adult surgery population, compared with 10 - 16 percent of the adult medicine population. The percent of total patients at Moderate severity of illness was almost the same for the two services, 35 to 46 percent for adult medicine and 35 - 42 percent for adult surgery.

A follow up analysis identified two All Patients Refined Major Diagnostic Categories (APR MDC) that contributed to the differences, Orthopedics (APR MDC 8) and Nutritional and Metabolic (APR MDC 10). In Orthopedics, the number of Minor severity resident discharges was 5462 for adult surgery and 542

### Table 2. Inpatient adult surgery discharges by severity of illness, Central New York Counties, 2017.

<table>
<thead>
<tr>
<th>Resident County</th>
<th>Number of Discharges</th>
<th>Percent of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minor</td>
<td>Moderate</td>
</tr>
<tr>
<td>Onondaga County</td>
<td>4151</td>
<td>4318</td>
</tr>
<tr>
<td>Cayuga County</td>
<td>526</td>
<td>635</td>
</tr>
<tr>
<td>Cortland County</td>
<td>343</td>
<td>432</td>
</tr>
<tr>
<td>Madison County</td>
<td>670</td>
<td>649</td>
</tr>
<tr>
<td>Oswego County</td>
<td>1111</td>
<td>1326</td>
</tr>
<tr>
<td>Tompkins County</td>
<td>465</td>
<td>571</td>
</tr>
<tr>
<td>Oneida County</td>
<td>2881</td>
<td>2568</td>
</tr>
<tr>
<td>Herkimer County</td>
<td>649</td>
<td>571</td>
</tr>
<tr>
<td>Jefferson County</td>
<td>985</td>
<td>888</td>
</tr>
<tr>
<td>Lewis County</td>
<td>247</td>
<td>223</td>
</tr>
<tr>
<td>St. Lawrence County</td>
<td>745</td>
<td>865</td>
</tr>
<tr>
<td>Total</td>
<td>12,773</td>
<td>13,046</td>
</tr>
</tbody>
</table>

Includes patients aged 18 years and over assigned to surgical APR Diagnosis Related Groups excluding obstetrics (APR DRGs 540 - 566) and mental health/substance abuse treatment (APR DRGs 740 - 776). Sources: New York Statewide Planning & Research Cooperative System (SPARCS) data.
for adult medicine. This difference was produced by joint procedures such as hip and knee replacements. In APR MDC 10, the comparison was 1123 resident discharges for adult surgery and 350 for adult medicine. The difference was produced by operating room procedures for obesity.

The study also included a review of resident hospital lengths of stay by severity of illness for each of the eleven counties in the region. For all of the eleven counties, the lengths of stay increased for each severity of illness category compared with the one before.

5. Discussion

During the 1970s and 1980s, government sponsored health planning in the United States focused attention on population-based use of services. Since that time, attention has shifted to provider specific utilization including severity of illness and other clinical indicators.

This case study evaluated the impact of severity of illness for hospital patients in the Central New York Health Service Area, one of the original health planning populations. It analyzed the impact of severity within resident populations, rather than by individual providers.

The study data demonstrated that patients at Extreme severity of illness, the highest level, constituted similar proportions of adult medicine, 6 - 13 percent, and adult surgery, 5 - 10 percent, in the eleven county region. This information suggested that the sizes of these outlier populations were similar. The data also suggested that the sizes of Moderate severity populations in the two services were similar, 35 - 46 percent in adult medicine and 35 - 42 percent in adult surgery.

The study data identified considerable differences in the sizes of Minor and Major severity of illness resident populations for the two services across the eleven county region. Patients at Minor severity accounted for 10 - 16 percent of adult medicine and 31 - 41 percent of adult surgery resident populations. Patients at Major severity accounted for 32 - 43 percent of adult medicine and 15 - 18 percent of adult surgery resident populations.

These differences resulted from large numbers of healthy patients in the adult surgery resident populations. Most of these inpatients were admitted for orthopedic procedures such as joint replacements and procedures to address obesity.

This analysis addressed the distribution of resident hospital inpatients by severity of illness in a single Health Service Area. Additional research, related to population health, should evaluate these indicators in additional health planning regions.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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- Case Reports in Clinical and Experimental Medicine
- Case Reports in Clinical and Experimental Metastasis
- Case Reports in Clinical and Experimental Nephrology
- Case Reports in Clinical and Experimental Ophthalmology
- Case Reports in Clinical and Experimental Optometry
- Case Reports in Clinical and Experimental Otorhinolaryngology
- Case Reports in Clinical and Experimental Pathology
- Case Reports in Clinical and Experimental Pharmacology and Physiology
- Case Reports in Clinical and Molecular Allergy
- Case Reports in Clinical and Translational Oncology
- Case Reports in Clinical Anesthesiology
- Case Reports in Clinical Apheresis
- Case Reports in Clinical Autonomic Research
- Case Reports in Clinical Biochemistry and Nutrition
- Case Reports in Clinical Biomechanics
- Case Reports in Clinical Cardiology
- Case Reports in Clinical Case Studies
- Case Reports in Clinical Child Psychology and Psychiatry
- Case Reports in Clinical Chiropractic
- Case Reports in Clinical Dentistry
- Case Reports in Clinical Effectiveness in Nursing
- Case Reports in Clinical Endocrinology and Metabolism
- Case Reports in Clinical Epidemiology
- Case Reports in Clinical Forensic Medicine
- Case Reports in Clinical Gastroenterology and Hepatology
- Case Reports in Clinical Genetics
- Case Reports in Clinical Haematology
- Case Reports in Clinical Hypertension
- Case Reports in Clinical Imaging
- Case Reports in Clinical Immunology
- Case Reports in Clinical Implant Dentistry and Related Research
- Case Reports in Clinical Interventions in Aging
- Case Reports in Clinical Laboratory Analysis
- Case Reports in Clinical Linguistics & Phonetics
- Case Reports in Clinical Lipidology
- Case Reports in Clinical Microbiology and Antimicrobials
- Case Reports in Clinical Microbiology and Infection
- Case Reports in Clinical Microbiology and Infectious Diseases
- Case Reports in Clinical Molecular Pathology
- Case Reports in Clinical Monitoring and Computing
- Case Reports in Clinical Neurology and Neurosurgery
- Case Reports in Clinical Neuropsychology
- Case Reports in Clinical Neuropsychology
- Case Reports in Clinical Neuroradiology
- Case Reports in Clinical Neuroscience
- Case Reports in Clinical Nursing
- Case Reports in Clinical Nutrition
- Case Reports in Clinical Obstetrics and Gynaecology
- Case Reports in Clinical Oncology and Cancer Research
- Case Reports in Clinical Oral Implants Research
- Case Reports in Clinical Oral Investigations
- Case Reports in Clinical Orthopaedics and Related Research
- Case Reports in Clinical Otolaryngology
- Case Reports in Clinical Pathology
- Case Reports in Clinical Pediatric Emergency Medicine
- Case Reports in Clinical Periodontology
- Case Reports in Clinical Pharmacology & Toxicology
- Case Reports in Clinical Pharmacy and Therapeutics
- Case Reports in Clinical Physiology and Functional Imaging
- Case Reports in Clinical Practice and Epidemiology in Mental Health
- Case Reports in Clinical Psychology and Psychotherapy
- Case Reports in Clinical Psychology in Medical Settings
- Case Reports in Clinical Radiology
- Case Reports in Clinical Rehabilitation
- Case Reports in Clinical Research and Regulatory Affairs
- Case Reports in Clinical Research in Cardiology
- Case Reports in Clinical Respiratory
- Case Reports in Clinical Rheumatology
- Case Reports in Clinical Simulation in Nursing
- Case Reports in Clinical Sleep Medicine
- Case Reports in Clinical Techniques in Small Animal Practice
- Case Reports in Clinical Therapeutics
- Case Reports in Clinical Toxicology
- Case Reports in Clinical Transplantation
- Case Reports in Clinical Trials
- Case Reports in Clinical Ultrasound
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