

Letters

AD ERRATUM

This table was omitted from the letter *The Microbiology of the Caman*, letters, UMJ Vo. 89, Number 2, September 2020, page 130

Table 1: Description of bacteria identified from camogie hurls and their clinical relevance

Bacteria identified	Clinical relevance & pathological involvement in infection
<i>Bacillus subtilis/vallismortis/amyloliquefaciens</i>	Soil organisms
<i>Bacillus altitudinis/pumilus</i>	Former: Opportunistic pathogen causing skin infection
<i>Brevibacterium iodinum</i>	Opportunistic pathogen. Natural host is soil
<i>Kytococcus sedentarius</i>	Opportunistic pathogen responsible for keratosis plantaris sulcatum and common amongst athletes. Also responsible for peritonitis and fatal haemorrhagic pneumonia
<i>Micrococcus luteus</i>	Opportunistic pathogen isolated from protective equipment in Japanese contact sport Kendo
<i>Morexella osloensis</i>	Opportunistic pathogen causing skin manifestations and also osteomyelitis
<i>Stenotropomonas rhizophila</i>	Isolated from the rhizosphere of oilseed rape and potatoes.

A RARE CASE OF NON-ISLET CELL TUMOUR HYPOGLYCAEMIA

Editor,

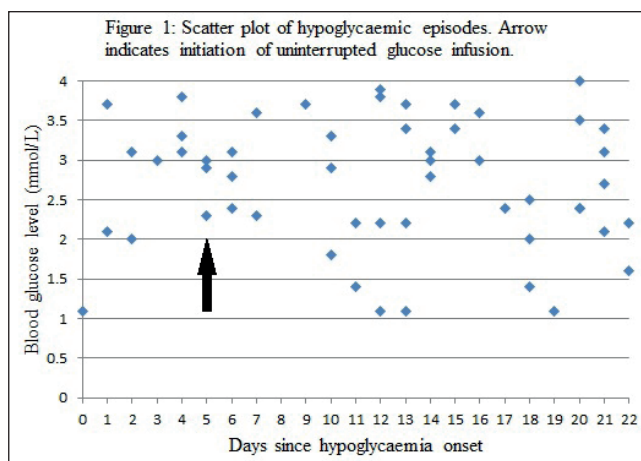
Non-islet cell tumour hypoglycaemia (NICTH) is a very rare paraneoplastic syndrome. The true incidence is unknown as many cases go undiagnosed. Only a few hundred cases are reported in English language medical literature since it was first described in 1929.¹ The following describes a case of NICTH.

A 75-year-old undergoing chemotherapy for advanced endometrial carcinosarcoma; was admitted after routine blood tests revealed a severe acute kidney injury. Endometrial carcinosarcoma is a rare type of uterine malignancy that is classified as a mixed epithelial and mesenchymal tumour. Renal function normalised rapidly after bilateral nephrostomies were inserted.

However, during convalescence the patient developed hypoglycaemic symptoms with a low blood glucose of 1.1mmol/L. This was unresponsive to oral glucose, so intravenous glucose was administered. There was no history of any endocrine disorder or any previous hypoglycaemia. Hypoglycaemic attacks then became more frequent and an uninterrupted 10% glucose infusion was needed, however this did not prevent hypoglycaemic episodes (Fig 1).

DIFFERENTIAL DIAGNOSIS

There was negligible suspicion of alcohol or exogenous insulin use. Other hypoglycaemic agents were ruled out by a medication review. Critical illness such as sepsis or liver failure seemed unlikely as inflammatory markers and liver function were unremarkable. Malnutrition was considered, however a dietician assessment reported adequate calorie intake. Adrenal insufficiency was ruled out with a normal Synacthen response. Insulinoma was excluded by suppressed serum insulin and C-peptide in the setting of hypoglycaemia



Parameter	Patient value	Normal value and/or interpretation
free thyroxine	17.6pmol/L	12-22pmol/L
thyroid stimulating hormone	1.22mIU/L	0.27-4.2mIU/L
cortisol response to Synacthen at 30minutes	643nmol/L	>450nmol/L
growth hormone	0.5ng/mL	suppressed
Whilst hypoglycaemic (blood glucose 2.3mmol/L)		
serum insulin	<3mU/L	2.6-24.9mU/L
C-peptide	0.5ug/L	1.1-4.4ug/L; indicating hypoinsulinaemic hypoglycaemia
Further investigations advised by endocrinology		
IGF1	3.8nmol/L	4.8-21.6nmol/L
IGF2: IGF1 ratio	21.8	<10; indicating NICTH



(Table 1). NICTH was considered once the above list of more common causes of hypoglycaemia had been excluded.

TREATMENT & OUTCOME

Calorie intake was optimised and steroid dosage was increased, but this had little effect in preventing hypoglycaemic episodes. The continuous glucose infusion was escalated to 20% glucose, however hypoglycaemia remained refractory. Interval imaging showed malignant disease progression and the options to treat her cancer with surgery, radiotherapy or chemotherapy had been exhausted. The patient died 22 days after the hypoglycaemic attacks began.

DISCUSSION

NICTH is a rare paraneoplastic condition that occurs due to tumoral over secretion of insulin-like growth factor 2 (IGF2). It occurs most commonly in patients with tumours of mesenchymal and epithelial origin.² IGF2 binds to insulin receptors which increases glucose uptake by skeletal muscle and inhibits glucose release from the liver. IGF2 also acts on the pituitary gland and pancreas to suppress the secretion of growth hormone and glucagon.³

In NICTH, the majority of overproduction is of 'big' IGF2 (a prohormone form of IGF2). This prohormone cannot easily be measured and only contributes a small fraction of the total IGF2 level. Therefore, total IGF2 may be reported as normal in NICTH. However, IGF1 is suppressed due to feedback inhibition and so the IGF2: IGF1 ratio is high. An IGF2: IGF1 ratio of greater than 10 confirms the diagnosis of NICTH.⁴

Only half the cases of NICTH have a known tumour at the onset of hypoglycaemia. The remaining half present with hypoglycaemia and a tumour is diagnosed later.⁵

Surgical removal of the tumour in NICTH is curative, however there is no consensus on the optimum strategy for managing inoperable patients. When surgical resection is not feasible, other antitumour therapies such as chemotherapy, radiotherapy or tumour embolization should be considered. In refractory cases, glucocorticoid steroids are the most commonly used medication used to treat NICTH.¹

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DELAFOXACIN, A NOVEL FLUOROQUINOLONE ANTIBIOTIC WITH ACTIVITY AGAINST HOSPITAL-, COMMUNITY- AND LIVESTOCK-ASSOCIATED METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA)

Editor,

Delafloxacin is a new fluoroquinolone antibiotic, approved for treatment of acute bacterial skin and skin structure infections (ABSSSIs) caused by both Gram-positive and Gram-negative organisms.¹ It recently received its regulatory licence from the European Medicines Agency in December 2019 (<https://www.ema.europa.eu/en/medicines/human/EPAR/quofenix>). For a seminal review on this background to this antibiotic, please see the recent seminal review by Mogle and colleagues.¹

As with any newly introduced antibiotic, it is important to evaluate a new antibiotic in the context of the local epidemiology and resistance rates, to aid physicians in the positioning of such a new antibiotic. To date, there have been no reports on the activity of delafloxacin against methicillin-sensitive (MSSA) and methicillin-resistant (MRSA) *Staphylococcus aureus*, within the Northern Ireland context, hence we wished to examine the *in vitro* susceptibility of MSSA and MRSA isolates to this new antibiotic.

Staphylococcus aureus (n=23) isolates [15 MSSA & 8 MRSA] were employed in this study, as detailed in Table 1. Isolates were obtained from the MicroARK Microbiology Culture Repository housed within the Northern Ireland Public Health Laboratory, Belfast City Hospital. Isolates within each category were selected at random for employment in this study. No other criteria were used in the selection of these organisms. Prior to use, all isolates were passaged twice by subculturing on Columbia Blood agar (Oxoid CM0031, Oxoid Ltd., Basingstoke, UK), supplemented with 5% (v/v) defibrinated horse blood for 24h at 37°C, under aerobic conditions. *In vitro* susceptibilities were examined on all 23 isolates, by employing Etest[®] gradient for delafloxacin (range:0.002-32 mg/L), as per manufacturer's instructions (Biomerieux Ltd., France) and in accordance with EUCAST methodology² and interpretive criteria.³ Susceptibility of



isolates to delafloxacin, as determined by the Minimum Inhibitory Concentration (MIC) value (mg/L), are quoted in Table 1.

Given the current EUCAST breakpoint for *S. aureus* sensitivity ($S \leq 0.25$ mg/L), none of the isolates tested were considered resistant to delafloxacin. Presently, there are no published reports of fluoroquinolone susceptibility to *S. aureus* solely in Northern Ireland, however when combined with data from England, the latest published ciprofloxacin resistance rates for 2018 in MSSA and MRSA bacteraemia were 5% and 62%, respectively.⁴

Delafloxacin is the latest addition to the fluoroquinolones in the antibiotic armamentarium. Early indications show that it may have a good *in vitro* susceptibility profile against *S. aureus*. In a study involving ABSSSIs in 1,042 patients from which 685 *S. aureus* isolates were recovered, delafloxacin MIC₉₀ values against levofloxacin-non-susceptible *S. aureus*, MRSA and MSSA isolates were all 0.25 µg/ml and where *S. aureus* was eradicated/presumed eradicated in 98.4% (245/249) of delafloxacin-treated patients. These

Phase 3 clinical trial data suggest that delafloxacin could be a good option for the treatment of infections caused by *S. aureus* isolates causing ABSSSIs, including MRSA isolates, where high rates of ciprofloxacin and levofloxacin non-susceptibility are observed.⁵

Physicians who think that the use of a fluoroquinolone may have a potential role in treating *S. aureus* infection in their patient should discuss options with their local microbiologist.

DECLARATION OF INTERESTS

The authors do not have any interests to declare. Delafloxacin E-test strips were kindly offered to hospitals throughout Europe (www.ihma.com) and were supplied gratis by Menarini Pharmaceuticals, Italy. Neither IHMA, nor Menarini Pharmaceuticals nor their agents were involved in study conceptualization, experimental design, experimental execution, data analyses, report writing nor had any role in the editorial process, funding or any other aspect of the study or writing.

Table 1: *In vitro* susceptibility of NI methicillin-sensitive and resistant *Staphylococcus aureus* to delofloxacin

Organism (Source)	Number of isolates Concentration (MIC) [mg/L]	Minimum Inhibitory	
		Mean	Range
<i>Staphylococcus aureus</i> (methicillin-sensitive; MSSA) Sputum isolates from adult patients with cystic fibrosis (CF)	8	0.043	<0.002-0.19
<i>Staphylococcus aureus</i> (methicillin-resistant: MRSA) Hospital-associated (from blood culture)	6	0.147	<0.002 - 0.25
Hospital-associated (zoonotic; canine)	1	0.19	0.19
Community-associated MRSA [CA-MRSA ST35, 5134, 5090, 4526, 4266 & 4388]	6	0.0233	<0.002 - 0.125
Livestock-associated MRSA LA-MRSA (porcine source) CC398 & CC30	2	0.05	0.006 - 0.094



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PERCEPTIONS OF MEDICAL STUDENTS ON UNDERGRADUATE BASIC SURGICAL SKILLS TRAINING

EDITOR,

Applications to surgical training programmes are on the decline^{1,2}. This is probably due to a combination of factors, including changes in undergraduate curricula and a gender shift in undergraduates. Despite the introduction of a

national undergraduate surgical curriculum, undergraduate training and proficiency in basic surgical skills (BSS) varies widely^{3,4}. We explored the impact of structured BSS workshops on undergraduate students' suturing confidence, interest in pursuing a surgical career and their perceptions of the importance of BSS training.

A qualitative analysis was undertaken of 193 medical students (68% female), ranging from years 1 to 5, attending seven standardised surgical skills workshops run by Scrubs student surgical society (Queen's University Belfast) between October 2018 and March 2019. Anonymous, pre-defined, 5-point Likert scale pre- and post-workshop questionnaires were used. The workshops included several basic surgical knots with instrumental and hand ties on both artificial and animal tissue models, as well as basic laparoscopic skills.

70% of students reported increased suturing confidence post-workshop (p<0.001) (Fig. 1). Additionally, 74% of students reported that the workshop had increased their interest in pursuing a surgical career.

Analysis of pre-workshop questionnaires of senior students (years 4-5, n=62) revealed that only 53% agreed (or strongly agreed) that they would be confident suturing a wound under direct supervision. 74% of senior students reported that they had no experience suturing in clinical practice.

Looking more broadly at undergraduate basic surgical skills training, 94% of students agreed (or strongly agreed) that BSS were important in the undergraduate curriculum. 97% of students agreed (or strongly agreed) that they would like to receive more BSS training in the future and 83% agreed (or strongly agreed) that this would have an influence on their future career choices.

This study has demonstrated that BSS training can increase student suturing confidence and boost interest in pursuing a surgical career. This is on the background of low levels of pre-workshop confidence and clinical experience of suturing in senior students. The power of these workshops to stimulate interest in surgery is likely due to three key factors. Firstly, gaining positive practical surgical experiences helps attract those interested in a hands-on specialty. Secondly, increased suturing confidence better equips students to participate more fully in surgical placements. Lastly, close interaction between demonstrators and students facilitates the development of role models and mentors, which is thought to be one of the main factors in directing career aspirations⁵.

Medical schools and student surgical societies should work together to ensure students receive sufficient high-quality BSS training. Material costs for running such workshops are low, however recruiting surgical demonstrators can be challenging. Better collaboration with surgical trainees could help address this issue. Trainees are motivated to gain teaching experience, have completed surgical skills courses, can provide clinical context to skills and are ideal role models for students.

In summary, simple structured BSS workshops can increase



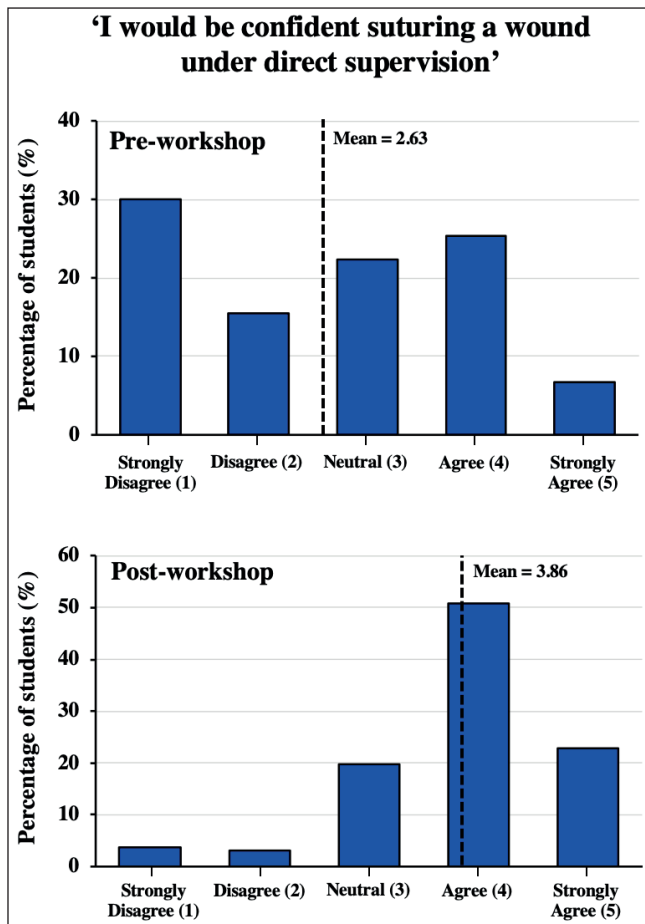


Figure 1. Pre- and post-workshop responses of students (n=193) to the statement 'I would be confident suturing a wound under direct supervision'

student confidence in essential surgical skills acquisition and increase interest in surgery as a career. Medical schools and student surgical societies should work together to improve undergraduate BSS training.

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A CURIOUS CASE OF GRANULOMATOSIS WITH POLYANGITIS

Editor,

A 65-year-old male non-smoker presented with a 2-month history of weight loss, fever and back pain. Bloods noted normocytic anaemia, elevated ESR (130mm/hr) and normal renal indices. To exclude malignancy, a CT chest, abdomen and pelvis was requested. This revealed a paravertebral mass extending from T6-T11 with significant uptake on subsequent CT-PET (Figure 1). CT guided biopsy was not possible due to the location of the mass. Endobronchial ultrasound guided biopsy of the mass was negative for malignancy, yet this

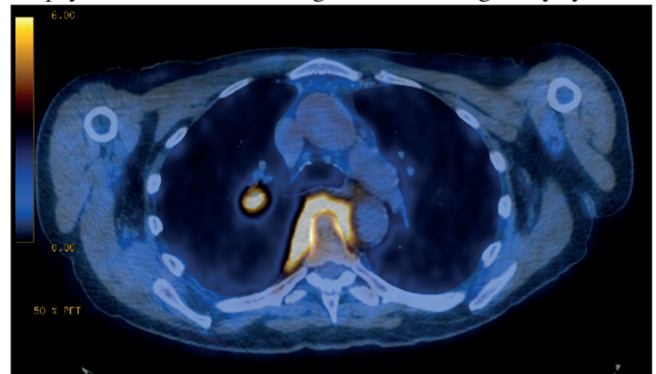


Figure 1: CT-PET showing uptake in the prevertebral and bilateral paravertebral region, (SUV max 11.92), PET avid right hilar nodes (SUX max 6.7) with encasement of the descending aorta, associated with increased uptake.

remained likely. Spinal referral was made for consideration of a biopsy/removal of the mass.

The patient was readmitted with acute kidney injury (urea 16.5mmol/L, creatinine 123µmol/L, eGFR 51ml/min). Presuming pre-renal failure, intravenous fluids were given with no improvement. Renal tract ultrasound was normal. Urine dipstick demonstrated significant blood and protein. Vasculitis screen showed PR3 ANCA of >8.0 and cANCA 20, prompting a presumptive diagnosis of granulomatosis with polyangitis (GPA). On renal biopsy, focal segmental glomerulosclerosis, active crescents and C3 positivity on immunofluorescence confirmed the diagnosis (Figure 2). Patient was pulsed with methylprednisolone before commencing oral cyclophosphamide and prednisolone. At 4 month follow up the patient's renal function had normalised and repeat imaging showed complete resolution of the mass.



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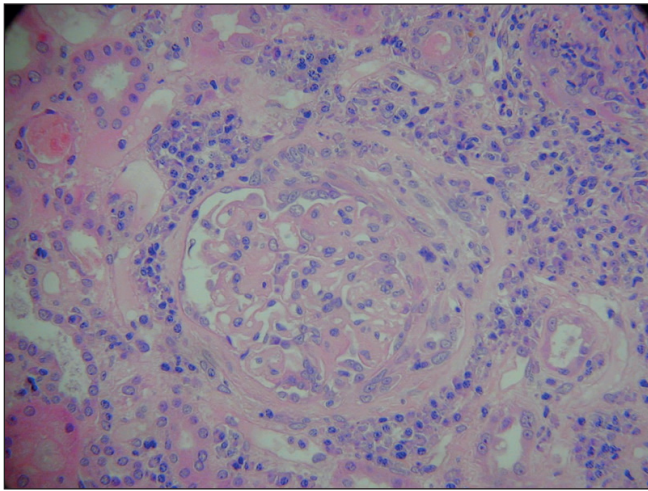


Figure 2: Histology showing rapidly progressive necrotising glomerulonephritis. In the image we can see crescents obliterating the glomerular space and fibrin deposits between proliferated cells. In the centre of the image compressed capillary loops are also seen.

These findings are classic for

Rapidly progressive glomerulonephritis.

GPA is a potentially lethal multisystem disorder of unknown aetiology which typically presents as a small-vessel vasculitis and necrotising granulomatous inflammation of the kidneys and respiratory tract. Anomalous manifestations exist with cutaneous, ocular, musculoskeletal, neurological and cardiac presentations previously described. GPA presenting as tumour like masses is less well documented. To date, GPA tumour like lesions have been noted in the orbits, nasal passages, lungs and right ventricle with a predilection for breast and renal masses.¹⁻³ Notably, there appears a close temporal association between GPA and renal cell carcinomas yet the immunopathologic mechanism remains unclear.⁴ Within the literature there exists only one previous case of GPA presenting as a paraspinal mass with this patient exhibiting synchronous renal and paraspinal masses.⁵ To the authors knowledge, our case represents the only description of a solitary GPA paraspinal mass.

Those with suspected GPA require serum anti-neutrophil cytoplasmic antibody (ANCA) testing. Whilst not wholly pathognomonic, elevated cANCA and PR3 levels strongly support a diagnosis of GPA in patients with moderate/high probability scores. A negative ANCA does not exclude the diagnosis therefore ANCA testing is not advised for monitoring disease activity. Definitive diagnosis requires evidence of necrotising vasculitis on biopsy. Many biopsy sites exist however renal samples are considered superior.

As per the European Renal Association and European Vasculitis Society, management of GPA is in accordance with symptom severity at diagnosis. 'Non organ threatening disease' requires treatment with methotrexate and glucocorticosteroids. Glucocorticoids with either cyclophosphamide or rituximab are recommended in "organ or life threatening disease" which includes tumour like lesions given their potential to compress surrounding structures. Plasma exchange is only required in the event of

pulmonary haemorrhage or rapidly progressive renal failure. This case highlights the diagnostic difficulty surrounding GPA and its ability to present as tumour like masses. In such cases it is imperative to exclude malignancy, yet this may generate diagnostic delays. The authors therefore argue GPA should be considered in any patient with a mass and evidence of multi-system disease.

Patient consent was obtained for the publication of this case.

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Conflicts of Interest: No conflicts of interest

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THINKING OUTSIDE OF THE LUNGS

Editor,

A 29-year-old female presented to the emergency department with increasing dyspnoea, a productive cough and pleuritic chest pain. She was a known intravenous drug user. On examination she was pyrexial with a temperature of 39.5 degrees and significantly hypoxic with PAO₂ of 8.6 kPa on FiO₂ of 0.6.

Admission blood test results showed a raised white cell count of 22.3 (10⁹/l), accompanying neutrophilia and raised C-reactive protein of 345.6 (mg/l). Liver function tests were also deranged.

Initial chest x-ray (Figure 1a) reported patchy opacification in the right mid zone, suggestive of infection and subsequent computed tomography (CT) of the chest revealed a patchy distribution of nodules and confluent pseudo-mass showing signs of cavitation with associated evidence of bilateral pleural effusions and reactive nodes in the right hilum and in mediastinum (Figure 1b).

She was commenced on broad spectrum antibiotics with

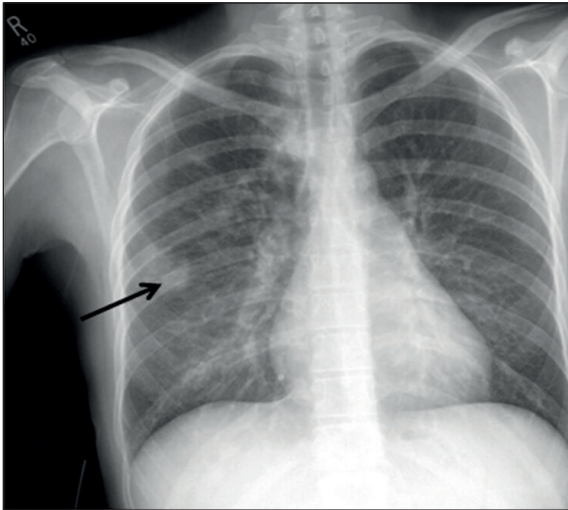


Figure 1a: Initial CXR showing patchy opacification in the right mid-zone (arrow)

minimal clinical improvement. On day 3, blood culture sampling revealed staphylococcus aureus bacteraemia, prompting transthoracic echocardiogram (TTE) which identified an echo bright, mobile structure on the atrial aspect of the tricuspid valve (Figure 2) with associated moderate to severe tricuspid regurgitation (peak flow gradient 47mmHg). A diagnosis of tricuspid valve endocarditis was confirmed.

Six weeks of intravenous antibiotics were completed during which the patient clinically improved and inflammatory markers normalised.

A follow-up trans-oesophageal echocardiogram (TOE) was performed at the end of treatment. There was no obvious vegetation and tricuspid regurgitation had improved to moderate. 2 years after initial presentation there have been no further clinical episodes of endocarditis.

Right sided infective endocarditis (RSIE) is infrequent compared to left sided infective endocarditis (LSIE), accounting for only 5-10% of IE cases.¹ The tricuspid valve is involved in 90% and staphylococcus aureus is the culprit organism in 70%.² RSIE is classically associated with IVUDU however congenital heart disease and intra-cardiac devices including pacemakers and intravascular catheters are also important risk factors.¹

The European Society of Cardiology describes the typical presentation of RSIE as fever, bacteraemia, and multiple septic pulmonary emboli, as in the case we have presented.⁴ This contrasts the systemic embolic events and vascular phenomenon seen in LSIE.⁴ Respiratory symptoms predominate and unless a high index of suspicion exists, this clinical picture could divert physicians towards a primary respiratory disease. Initial misdiagnosis poses a risk of premature antibiotic delivery, firstly potentially concealing a microbiological diagnosis that may prompt a consideration of IE and secondly preventing subsequent sensitivities to assist in antibiotic choice.

Diagnostic delay may also increase complications including valvular destruction, pulmonary abscess and empyema.² Damage to pulmonary vasculature increases the risk of pulmonary haemorrhage.² On this basis we hope that this case will prompt physicians to consider a diagnosis of RSIE



Figure 1b: CT chest showing a confluent pseudo-mass with cavitation (arrow)

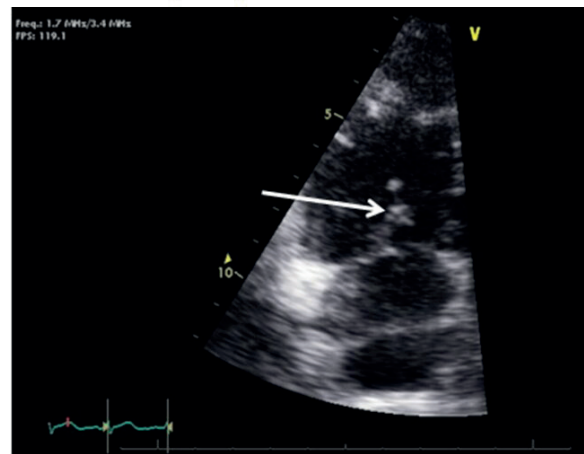


Figure 2: Echocardiogram showing vegetation on the atrial aspect of the tricuspid valve (arrow).

when presented with acute respiratory illness.

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