PRISM SECTION
(Patients’ Revelations as Insightful Studies of their Management)

• Acyclovir Neurotoxicity In A Patient With End-stage Renal Failure Undergoing Continuous Ambulatory Peritoneal Dialysis — A Case Report And What Can Be Learnt
• A Case Of Chikungunya Masquerading As Dengue
ACYCVLOR NEUROTOXICITY IN A PATIENT WITH END-STAGE RENAL FAILURE UNDERGOING CONTINUOUS AMBULATORY PERITONEAL DIALYSIS — A CASE REPORT AND WHAT CAN BE LEARNT

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Renal Failure (ESRF) receiving Continuous Ambulatory Peritoneal Dialysis (CAPD) was admitted acutely for altered mental status and neurological symptoms. She had been initiated on CAPD for ESRF secondary to Type 2 diabetic nephropathy 5 months earlier, and CAPD had been uneventful so far. Her other medical problems include hypertension, dyslipidaemia and gouty arthritis.

She presented to the Emergency Department with bilateral upper limb weakness and clumsiness, bilateral lower limb weakness for 1 day’s duration. There were no complaints of altered sensation or bladder and bowel symptoms. In addition, her family members reported altered behaviour for the previous 1 day, and described the patient as being “disoriented” and “not herself”. There was no history of fever, headache, fall, head injury or trauma. Significantly, she had had a painful vesicular rash affecting her left lower limb for the previous 3 days, for which she was diagnosed with herpes zoster 2 days earlier by a family physician, for which she was started on oral acyclovir.

Our patient was diagnosed as having acyclovir toxicity and commenced on urgent haemodialysis. Her symptoms resolved completely after 2 days. Our case details the uncommon but potentially fatal complication of acyclovir toxicity in patients with renal impairment, reinforces the importance of dose reduction in these patients and demonstrates haemodialysis as a good form of treatment for acyclovir toxicity. Family physicians should be familiar with dose adjustments for common medications prescribed to ESRF patients in the outpatient setting as the burden of chronic kidney disease increases in Singapore.

Keywords: Acyclovir Neurotoxicity, Dialysis, Zoster

INTRODUCTION

Herpes zoster is a relatively common condition diagnosed in general practice in Singapore, for which oral acyclovir is widely used for treatment with generally good results. Acyclovir neurotoxicity is a known entity which has been reported infrequently, and is known to occur more commonly with intravenous treatment than with oral treatment and in patients with ESRF.1 The half-life of acyclovir is prolonged in patients with ESRF, predisposing these patients to acyclovir toxicity, including neurological side effects. Dose adjustment is recommended for patients with ESRF on dialysis.2 We report a case of acyclovir neurotoxicity in a patient undergoing CAPD.

PATIENT’S REVELATION: WHAT HAPPENED?

A 65-year-old, community-ambulant lady with End-Stage Renal Failure (ESRF) receiving Continuous Ambulatory Peritoneal Dialysis (CAPD) was admitted acutely for altered mental status and neurological symptoms. She had been initiated on CAPD for ESRF secondary to Type 2 diabetic nephropathy 5 months earlier, and CAPD had been uneventful so far. Her other medical problems include hypertension, dyslipidaemia and gouty arthritis.

Our patient received 4 hours of urgent haemodialysis on the same day of admission via a temporary right internal jugular vein catheter. Six hours after completion of haemodialysis,
there was rapid recovery of symptoms and the lumbar puncture was not performed. By the end of her second day in hospital, after 2 sessions of 4-hour-long haemodialysis, neurological recovery was complete. Our patient received a total of 3 haemodialysis sessions, each lasting 4 hours. She was observed a further 24-48 hours and remained symptom free. Her vesicular rash was also starting to dry and form crusts. She was discharged home after 5 days in hospital. Her clinical findings of herpes zoster with complete resolution of neurological symptoms after haemodialysis strongly support our diagnosis of acyclovir neurotoxicity.

GAINING INSIGHT

What is the acute diagnosis in this patient and how might this impact the initial management?

Epidemiological studies have identified a risk of 0.5 – 1 percent for meningitis or cerebral vasculitis developing in patients with herpes zoster. This risk may be increased in immunocompromised individuals, such as those with diabetes mellitus or ESRF. There have been sporadic reports of herpes zoster-associated encephalitis among patients with ESRF on CAPD, for which diagnosis was made based on CSF examination and electroencephalography (EEG), and after the patient had improved with escalation of acyclovir from oral to intravenous route.

In all cases of herpes zoster with neurological symptoms, herpes zoster-associated encephalitis should be excluded. The gold standard for diagnosis of herpes zoster-associated encephalitis is currently PCR to demonstrate the presence of the herpes simplex virus. However, in a patient with known renal impairment who has received acyclovir treatment, the timeline of events may suggest a diagnosis of acyclovir neurotoxicity instead. In our patient, astute clinical judgement expedited the appropriate management in terms of organising haemodialysis immediately and prevented time wastage, risks involved and costs of a lumbar puncture at initial presentation. However, the managing team and authors recognise that the inclusion of CSF results showing the absence of herpes simplex virus would lend weight to the diagnosis of acyclovir neurotoxicity.

Neurotoxic side effects of acyclovir have been described since the early 1980s. Since approximately 90 percent of the drug is renally excreted, half-life and serum levels of acyclovir are markedly elevated in renal disease. A range of symptoms, from tremor to coma, have been described, with typical onset 24 to 72 hours after both oral and intravenous acyclovir. Visual hallucinations and death delusions are striking features in patients prescribed acyclovir with previously normal brain function. In patients with presumed encephalitis, failure to consider acyclovir neurotoxicity may lead to misinterpretation of neuropsychiatric symptoms as worsening encephalitis; precipitating inappropriate dose increases, rather than reduction or withdrawal.

MANAGEMENT

Clinical applications for the inpatient doctor, emergency physician and family physician seeing this patient

Acyclovir is especially poorly removed by peritoneal dialysis and, in CAPD patients, neurotoxicity has been reported in the presence of high serum drug levels, even when recommended reduced doses were administered. In one study evaluating oral dosage of acyclovir in CAPD patients, supratherapeutic concentrations for all participants were found when following the recommended dose. There is, however, a lack of relationship between plasma concentration of acyclovir and the onset of symptoms. Tremors, disorientation, agitation, hallucinations, and delirium are common presentations of acyclovir-induced encephalopathy, whereas seizures, cerebellar ataxia, sensory symptoms, speech disorders, fever, and cranial nerve palsies are much less frequent. Criteria supporting acyclovir neurotoxicity include a temporal association between the symptoms and acyclovir use, as well as acellular CSF.

Haemodialysis can remove up to 45 percent and 113 ml/min of acyclovir and this is considered a reasonable method to reduce the duration of toxicity. It should also be noted that the resolution of the syndrome can be delayed by 48–72 hours after clearance of the drug. Acyclovir neurotoxicity has been reported even in patients receiving doses considered adequate. This may be due to variable individual susceptibility to the drug. Although not done in this patient, the authors suggest serum acyclovir monitoring to document response and improvement in condition, in accordance with studies done on acyclovir toxicity although this is not a substitute for frequent assessment of the patient’s clinical response.

A literature review on PubMed among ESRF patients on dialysis with herpes zoster who received acyclovir and subsequently developed acyclovir toxicity yielded few results. There has been sporadic reporting of cases of acyclovir neurotoxicity in ESRF patients who subsequently required haemodialysis for removal of the drug — 2 cases of patients on CAPD were reported in 1992, for which 1 unfortunately died; and 3 cases of patients on haemodialysis were reported from 1995–2004. There have also been a few studies documenting valacyclovir toxicity in ESRF patients in recent years from 2012–2014. The bioavailability of valacyclovir is 54 percent compared to approximately 20 percent for oral acyclovir and it is also eliminated renally, hence it is postulated that toxicity may occur more frequently in ESRF patients taking valacyclovir.

Usual methods of CAPD provide relatively low drug clearances during any given dialysate exchange, as compared to haemodialysis. There are available guidelines such as those from the Nephrology Pharmacy Associates which guide physicians on which drugs may require additional or decreased dosing while on peritoneal dialysis or haemodialysis. Family physicians should be aware of the presence of these guidelines and how to access them as these can have an effect on
prescribing habits for common drugs. As an example, the removal of the commonly prescribed acetaminophen from the body is enhanced with haemodialysis but not peritoneal dialysis and there is suggestion that supplemental dosing in conjunction with dialysis is usually required.\textsuperscript{1,24}

There were 4,169 patients on dialysis in Singapore by 2008. This number represented an 89 percent increase since end-1998, when there were 2,209 patients on dialysis. The incidence of new ESRF patients requiring dialysis increases every year, from 564 new cases in 1998 to 1,212 cases in 2008. This represents a 115 percent increase during this 10-year period.\textsuperscript{25,26,27} With a rapidly ageing population, Singapore can expect an increasing burden of ESRD and more of these patients will be presenting to the outpatient setting. Globally, it is estimated that there are currently more than 2 million people on renal replacement therapy to sustain life, and this likely represents less than 10 percent of those who need it.\textsuperscript{28} In view of this, the role of Family Physicians and General Practitioners in managing patients with ESRD will grow and we encourage all doctors to be aware of potential problems with regard to toxicity in patients with impaired renal function as illustrated by this case of acyclovir neurotoxicity.

CONCLUSION

Our patient demonstrates the clinical significance of acyclovir neurotoxicity in an ESRF patient on CAPD. Herpes zoster is a common condition seen in ambulatory practice locally. It is important for family physicians to consider the patient’s comorbidities before prescribing acyclovir and adjust doses accordingly in the setting of renal impairment. The current acceptable maximum daily dose of oral acyclovir for treatment of herpes zoster for patients with a creatinine clearance of less than 10ml/min is 800mg every 12 hourly.\textsuperscript{29} As acyclovir neurotoxicity can occur with a wide range of doses, it is imperative to monitor the patient closely and exercise clinical judgement even after dose adjustment.

REFERENCES

He presented to the ED due to persistence of the fever (4th day) and a sudden onset of a non-pruritic rash distributed over his chest and back. He was concerned about whether the GP had made a misdiagnosis and if he required antibiotics.

He described his fever as having intermittent spikes with a maximum temperature of 38.9°C that was associated with myalgia and generalised lethargy. His retro-orbital pain had resolved and there were no visual disturbances. He did not have any chills, rigors, arthralgia, bleeding tendencies nor abdominal pain, and there was no change in urinary or bowel habits. There was no cough, rhinorrhea or breathing difficulty.

Travel and social history
Three days prior to the start of his fever, he had visited a forested area at the southern ridges in Singapore with his friends. He had also travelled to Thailand, Laos and Vietnam for jungle trekking two months earlier and visited the Philippines one month earlier and Malaysia three weeks earlier for a holiday. He remained asymptomatic then and did not remember being bitten by any insect or animal. He had no significant contact history. He was sexually active but denied unprotected sex. He did not consume any illicit drugs or participate in intravenous drug abuse.

Physical findings at presentation to the ED
His temperature was 38.1°C, blood pressure was 120/81 mmHg and heart rate was 88 beats per minute. He was alert with no pallor or jaundice. He did not have any epistaxis, gum bleeding or bruising. A blanchable maculopapular rash was noted over his chest and back with islands of sparing. There were no lesions on his palms and soles. Examination of the oropharynx was normal. Heart sounds were dual and he had vesicular breath sounds. His abdomen was soft, non-tender and there was no hepatosplenomegaly. No lymph nodes were palpable.

Progress
The progress of illness is shown in Figure 1 on the timeline of events. The patient was subsequently admitted to the general ward with the provisional diagnosis of viral fever with thrombocytopenia for investigation.

Investigations
The following investigations were done in the hospital on admission:

- Dengue duo test:
  - Dengue NS1: Negative.
  - Dengue IgM: Negative.
  - Dengue IgG: Negative.

- Malaria microscopy: No malaria parasite seen.
Chikungunya IgM: Ordered on admission, results available the next day showed IgM positive.

Full blood count:
- Haemoglobin: 15.0g/dL (12.9 - 17.0).
- White Blood Cell: 3.77x10^9/L (3.40 - 9.60).
- Platelets: 78x10^9/L (132 - 372).
- Haematocrit: 42.5% (37.5 - 49.3).
- Lymphocytes: 1.71x10^9/L (0.94 - 3.08).

Liver function test: Normal.

Tests for differential diagnoses of leptospirosis, hepatitis viruses (A, B, C), cytomegalovirus, Epstein Barr virus and human immunodeficiency virus infections done later in the general ward were also negative. Blood and urine cultures did not show any growth of organisms and his chest X-ray was normal.

With the positive results of chikungunya infection, the patient was informed that he did not have a dengue infection. He was later discharged with antipyretics and given a follow-up appointment with his GP to monitor his platelet counts.

**GAINING INSIGHT**

This patient presented with fever for 4 days. He asked, “Why is the fever lasting this length of time? Are the blood tests accurate? Is my condition serious and do I need to be admitted to the hospital?”

**MANAGEMENT**

The management of this case can be discussed as phases:

1. **Before the diagnosis of the chikungunya infection**

   The GP who had initially seen the patient had given him instructions to return for a review and to watch out for warning signs such as bleeding and abdominal pain. Furthermore, even though the dengue duo test performed was sensitive and specific, positive detection rate is not 100 percent in cases of secondary dengue (defined as dengue infection in a host that has previously been infected by a dengue virus, or after non-dengue flavivirus vaccination or infection). This was shown in the paper by Wang et al., where the positive detection rate by dengue duo assay for secondary dengue was only 90 percent.

   In the hospital, the patient was informed that although the initial dengue test was negative, there was still a possibility of false-negative results. Moreover, as he had fever, myalgia, rash, lethargy and thrombocytopenia, he had fulfilled the 2009 WHO criteria for probable dengue with warning signs (see Table 1). Furthermore, due to his significant travel history to multiple countries, additional tests for other offending organisms would also be performed together with the repeat dengue test.

   Although he did not have leukopenia or a raised haematocrit, he was admitted to the hospital to monitor for signs of shock and haemorrhage. This was in view of his lethargy and falling platelet level, which are warning signs that predict a higher risk of progression to severe dengue. He was also monitored for a drop in postural blood pressure which he did not have. The patient was treated symptomatically with paracetamol and the administration of intravenous fluids (2.5 litres was given over 24 hours).

   The repeat dengue duo test (utilising the SD BIOLINE Dengue Duo kit) was negative. Thus, the diagnosis of dengue fever was very unlikely, given the high sensitivity and specificity of the test as seen in Table 2.
A CASE OF CHIKUNGUNYA MASQUERADING AS DENGUE

Table 1: 2009 WHO classification for diagnosing dengue

<table>
<thead>
<tr>
<th>Dengue without warning signs</th>
<th>Dengue with warning signs (requires strict observation and medical intervention)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever and two of the following:</td>
<td>Dengue (as defined above) with any of the following:</td>
</tr>
<tr>
<td>1. Nausea, vomiting</td>
<td>1. Abdominal pain or tenderness</td>
</tr>
<tr>
<td>2. Rash</td>
<td>2. Persistent vomiting</td>
</tr>
<tr>
<td>3. Aches and pains</td>
<td>3. Clinical fluid accumulation (ascites, pleural effusion)</td>
</tr>
<tr>
<td>4. Leukopenia</td>
<td>4. Mucosal bleeding</td>
</tr>
<tr>
<td>5. Positive tourniquet test</td>
<td>5. Lethargy, restlessness</td>
</tr>
<tr>
<td></td>
<td>6. Liver enlargement &gt;2 cm</td>
</tr>
<tr>
<td></td>
<td>7. Laboratory: increase in haematocrit concurrent with rapid decrease in platelet count</td>
</tr>
</tbody>
</table>

Severe Dengue

Dengue with at least one of the following criteria:

1. Severe plasma leakage leading to:
   - Shock (Dengue Shock Syndrome)
   - Fluid accumulation with respiratory distress
2. Severe bleeding as evaluated by clinician
3. Severe organ involvement
   - Liver: AST or ALT ≥ 1000
   - Central nervous system: impaired consciousness
   - Failure of heart and other organs

Table 2. Sensitivity and specificity of dengue duo test

<table>
<thead>
<tr>
<th></th>
<th>Dengue NS1 Ag</th>
<th>Dengue IgG/IgM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>92.4%</td>
<td>94.2%</td>
</tr>
<tr>
<td>Specificity</td>
<td>98.4%</td>
<td>96.4%</td>
</tr>
</tbody>
</table>
Table 3. A comparison of typical chikungunya and dengue features with this case

<table>
<thead>
<tr>
<th>Feature</th>
<th>Chikungunya</th>
<th>Dengue</th>
<th>This Case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (&gt;39°C)</td>
<td>+++</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>+++</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Arthritis</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Headache</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Rash</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Myalgia</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>+/-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Shock</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>+++</td>
<td>++</td>
<td>-</td>
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<tr>
<td>Neutropenia</td>
<td>+</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>+</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Haemoconcentration</td>
<td>-</td>
<td>++</td>
<td>-</td>
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</tbody>
</table>

Source: CDC factsheet 2014. Chikungunya: Clinical management in dengue-endemic areas.

(2) After the diagnosis of chikungunya infection

The patient was informed that he had chikungunya fever diagnosed by a blood test and that he did not have dengue fever. It was evident that he had been infected in Singapore given his travel history and the incubation period of the chikungunya virus (2 to 4 days). Moreover, chikungunya infection is endemic in Singapore. His concerns and anxieties were also allayed by explaining that no antibiotic was required and that the fever would eventually resolve.

(3) Closure

As he remained haemodynamically stable throughout his hospital stay and showed clinical improvement with a rising platelet trend, he was discharged on day 6 of his illness. He was arranged to follow up with his GP and told that he could return to school but to watch out for red flags such as bruising, gum bleeding, giddiness, severe vomiting, diarrhoea and abdominal pain. Additionally, he should avoid sports and strenuous physical activity until his platelet levels normalized. To prevent further transmission of the disease, he was advised to protect himself and household members from mosquito bites during this period.

On day 7 of his illness, he was reviewed by the GP and his platelet count had increased to 108x10^9/L. He had full resolution of his symptoms and has been well since.

DISCUSSION

(1) Atypical features in this case

This case highlights the patient’s journey in a chikungunya infection presenting atypically. For a while the quandary was: Is this dengue?

The features in this case were different from typical cases in the following ways — the onset of fever was more gradual than acute, the duration of fever was longer than expected, there was no arthralgia and thrombocytopenia was noted to be below 100x10^9/L.

In Table 3, this case is compared with the typical clinical and laboratory features of chikungunya and dengue infections based on the American Centers for Disease Control and Prevention (CDC) factsheet. Although Table 3 seems to suggest that haemoconcentration and shock are distinguishing features between chikungunya and dengue, one should bear in mind that they both occur in severe dengue. Since most cases of dengue fever in Singapore are not severe, haemoconcentration and shock may not be useful distinguishing features in this patient.

It is also important to note that there are other atypical or severe disease presentations of chikungunya fever that have been reported involving various systems — neurological (meningoencephalitis), ocular (iritis), cardiovascular (myocarditis), dermatological (vesiculobullous dermatosis), hepatic (acute hepatitis), and renal (nephritis). These are more common in children and the elderly.

(2) Known typical clinical features of chikungunya infection

The typical features of both chikungunya fever and dengue
fever have been described in the CDC factsheet 2014 (see Table 3).

Table 4 shows a comparison of these features from different studies conducted locally and overseas. It can be seen that almost all patients had fever and arthralgia. In a prospective cohort study in Singapore, patients with chikungunya fever with persistent arthralgia tended to be females. The calculated percentages for the whole series are shown in the last column.

(3) Reports of similar cases in the literature
A local study found that although key significant differences existed between dengue and chikungunya infection, there were substantial overlaps in the symptoms and signs. The key differences that were most apparent at presentation were leukocytosis, myalgia and arthralgia in chikungunya cases, compared to thrombocytopenia in dengue cases.

(4) Dual infection

Moreover, one must also be aware that the two diseases can also be seen simultaneously in the same patient.

(5) Manage as dengue until chikungunya infection is confirmed

It is important to distinguish chikungunya fever from dengue fever as the latter has the potential for considerably worse outcomes, including death. Where the illness is prolonged, sustaining the patient’s confidence is important. Although differentiation of chikungunya from dengue may not alter supportive management, it would be useful in the diagnosis and advice to patients of the expected clinical course. This patient had initially seen a GP but later ended up in the tertiary hospital on his own accord due to his concern over his fever and sudden appearance of his rash. Informing the patient of the likely disease progression and on the red flags to seek medical attention will empower the patient and allay concerns. When faced with a diagnostic dilemma, close follow up and vigilance to pick up new signs and symptoms on the physician’s part is also required.

Finally, since January 2008, Singapore has experienced autochthonous transmissions of chikungunya virus in areas where Aedes albopictus and Aedes aegypti mosquitoes were present and has suffered 2 major outbreaks in 2008 and 2013. As such, vector control is extremely important and remains the sole method for reducing transmission of chikungunya as no vaccine is currently available. Physicians must do their role in educating patients about safeguard measures and source reduction methods to control the spread of mosquito-borne diseases.

**CONCLUSION**

(1) This case highlights similarities between chikungunya and dengue infections, and the difficulty in distinguishing the two by symptoms and signs alone.

(2) This case also highlights the importance of managing the patient as having dengue until dengue has been excluded.

**REFERENCES**

