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REVIEW

Pharyngeal-cervical-brachial variant of Guillain–Barré syndrome

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Received 14 March 2013

Revised 21 May 2013

Accepted 25 May 2013

Published Online First

26 June 2013

ABSTRACT

The pharyngeal-cervical-brachial (PCB) variant of Guillain–Barré syndrome is defined by rapidly progressive oropharyngeal and cervicobrachial weakness associated with areflexia in the upper limbs. Serial nerve conduction studies suggest that PCB represents a localised subtype of Guillain–Barré syndrome characterised by axonal rather than demyelinating neuropathy. Many neurologists are unfamiliar with PCB, which is often misdiagnosed as brainstem stroke, myasthenia gravis or botulism. The presence of additional ophthalmoplegia and ataxia indicates overlap with Fisher syndrome. Half of patients with PCB carry IgG anti-GT1a antibodies which often cross-react with GQ1b, whereas most patients with Fisher syndrome carry IgG anti-GQ1b antibodies which always cross-react with GT1a. Significant overlap between the clinical and serological profiles of these patients supports the view that PCB and Fisher syndrome form a continuous spectrum. In this review, we highlight the clinical features of PCB and outline new diagnostic criteria.

INTRODUCTION

Patients with the pharyngeal-cervical-brachial (PCB) variant of Guillain–Barré syndrome (GBS) typically present with rapidly progressive oropharyngeal and cervicobrachial weakness associated with areflexia in the upper limbs. Power in the lower limbs is usually preserved or only mildly affected, indicating that PCB represents a localised subtype of GBS.^{1,2} Very often patients presenting with PCB are initially misdiagnosed as having brainstem stroke, myasthenia gravis or botulism, which can often be excluded on clinical history and examination alone. Clinical, immunological and neurophysiological studies have shown that PCB forms a continuous spectrum with Fisher syndrome (FS) and represents a localised form of axonal GBS.^{2–5} In this review, we highlight the clinical features of PCB and how these relate to our current understanding of its pathophysiology. We also present new diagnostic criteria with the aim of increasing awareness among neurologists and physicians.

ORIGINAL DESCRIPTION

In 1986, Ropper¹ described three patients who developed rapidly progressive oropharyngeal, neck and shoulder weakness, in the absence of sensory disturbance and with relative sparing of the lower limbs, which mimicked the descending paralysis seen in botulism (table 1). Patient 1 developed swallowing difficulties and blurred vision 10 days after upper respiratory infectious symptoms and was intubated early due to retention of carbon dioxide.

By day 3, there was ptosis and marked facial and oropharyngeal weakness. Ocular abduction was impaired bilaterally and pupils were noted to be dilated and sluggish. On day 5, neck and proximal arm weakness became evident but the legs remained spared. Absent tendon reflexes were noted in the upper limbs only. After 1 month, there was significant improvement and by 6 months power had returned to normal. Patient 2 also presented with swallowing difficulties and was intubated early due to excessive secretions. Subsequent asymmetrical ptosis, mild facial, neck and proximal limb weakness all developed rapidly in the absence of ophthalmoplegia and by 4 months had nearly completely resolved. Patient 3 was described in less detail but also developed PCB weakness in association with ptosis in the absence of ophthalmoplegia.

Botulism, which is also characterised by ptosis, internal and external ophthalmoplegia, bulbofacial weakness and symmetrical descending flaccid paralysis, was considered, but excluded on the basis of laboratory findings. Unlike botulism, two of Ropper's patients (Patients 2 and 3) had elevated cerebrospinal fluid (CSF) protein. Patient 1 had normal CSF protein on day 3 and was later found to have no evidence of botulinum toxin. Patient 1 also had normal nerve conduction studies (NCS), which when repeated 2 days later showed prolongation of F-wave latencies. In Patient 2, there was mild slowing of the median nerve motor conduction velocities and absent sensory action potentials in the arms. Ropper concluded that PCB probably represented a regional variant of GBS.

Several years later, Ropper described a fourth case.³ This patient presented with dizziness and imbalance, followed the next day by paraesthesias in toe and then finger tips. By day 3, she had moderate PCB weakness and mild facial and proximal leg weakness and absent deep tendon reflexes in all four limbs. She was ataxic and had difficulty walking. There was additional ptosis, absent pupillary response to accommodation and absent upgaze with mild bilateral abduction failure. CSF was normal and NCS showed absent F-waves. She required intubation but made a full recovery by week 4. He attributed this to PCB overlap with FS because of ophthalmoparesis and ataxia.

CLINICAL FEATURES

The findings of a prospective study of more than 250 patients with GBS done at the Massachusetts General Hospital showed that FS (5%) was the most frequent GBS variant with PCB (3%) a second.⁶ Here we highlight the clinical features based on the

To cite: Wakerley BR,
Yuki N. *J Neurol Neurosurg
Psychiatry* 2014;**85**:
339–344.

Table 1 Case reports of pharyngeal-cervical-brachial (PCB) variant of Guillain-Barré syndrome and our diagnosis based on the clinical features

	Ropper ¹		Ropper ³	Mizoguchi et al ⁹	Kashihara et al ¹⁰	Osaki et al ¹¹	Okuda et al ¹²	Pan et al ¹³	Arai et al ⁴		Capasso et al ¹⁴		Chan et al ⁵
	Patient 1	Patient 2							Patient 1	Patient 2	Patient 1	Patient 2	
Age, sex	19, M	54, F	23, F	40, M	55, F	26, M	21, M	37, F	65, M	41, M	47, M	67, M	61, F
Prosis	+	+	+	-	+	+	-	-	-	-	-	-	+
External ophthalmoparesis	+	-	++	+	+	+	-	-	-	+	-	-	++
Internal ophthalmoparesis	+	-	-	-	+	-	-	-	-	-	-	-	-
Facial palsy	++	+	+	+	+	+	+	+	++	+	++	++	-
Oropharyngeal palsy	++	++	++	++	++	++	++	++	++	++	++	++	++
Neck weakness	++	++	++	++	++	++	++	++	++	++	++	++	++
Upper limb	++	+	++	-	+	+	+	+	++	+	++	+	+
Weakness	+	+	+	+	-	+	+	-	-	+	+	+	-
Hypo- or areflexia	-	+	+	-	+	+	+	-	+	+	-	+	+
Lower limb	-	-	+	-	-	-	-	-	-	-	-	-	+
Our diagnosis	PCB	PCB	PCB/FS	PCB	PCB	PCB	PCB	PCB	PCB	PCB	PCB	PCB/AAN	PCB/FS

-, normal; +, mild ophthalmoplegia or weakness; ++, marked ophthalmoplegia or weakness; /, overlap syndrome. AAN, acute ataxic neuropathy; FS, Fisher syndrome.

largest case series which examined 100 patients with PCB and its overlap syndromes in Japan.² Median age was 43 years (range 5–83 years) with a slight male preponderance (male:female 1.3:1). Antecedent upper respiratory tract infectious symptoms and diarrhoea were observed in 71% and 30% of patients respectively and similar to GBS, 31% had serological evidence of *Campylobacter jejuni* infection, whereas, cytomegalovirus (6%), Epstein-Barr virus (4%), *Mycoplasma pneumoniae* (3%) and *Haemophilus influenzae* (1%) were less common.

In keeping with Ropper's original description,¹ Nagashima et al² defined 'pure' PCB in patients presenting with rapidly progressive oropharyngeal and cervicobrachial weakness associated with hyporeflexia or areflexia in the absence of ophthalmoplegia or leg weakness. In contrast to Ropper's cases, sensory disturbance in the upper limbs was also noted in nearly two-thirds of patients in the more recent series.² Some patients also displayed normal or exaggerated reflexes, which is apparent in about 10% of GBS patients during disease course,⁷ and were defined as having 'PCB with preserved muscle stretch reflexes'. Nosological classification can be confusing because GBS forms a continuum of overlapping syndromes. Patients therefore presenting with features in addition to PCB weakness, including: ophthalmoplegia and ataxia; ophthalmoplegia, ataxia and altered consciousness; or leg weakness were defined as PCB overlap with Bickerstaff brainstem encephalitis (BBE) or GBS respectively.

In agreement with the previous two authors,^{2, 3} we suggest that patients who develop ophthalmoparesis and ataxia should be defined as having PCB overlap with FS and that patients with additional altered consciousness should be defined as having PCB overlap with BBE. Although 'pure' PCB can be reserved for patients presenting with isolated oropharyngeal weakness, neck weakness and arm weakness, in order to avoid confusion and based on the neurophysiological features of PCB, we suggest that patients previously defined as having 'PCB overlap with GBS'² are redefined as having just PCB, albeit a more extensive form. This is because, as described later in this review, PCB is thought to represent a focal form of acute motor axonal neuropathy (AMAN) and to our knowledge cannot occur in conjunction with acute inflammatory demyelinating polyneuropathy (AIDP). This is illustrated in a patient who initially presented with acute weakness in all four limbs who developed prominent PCB weakness in the recovery phase,⁸ and suggests that some GBS patients who present with tetraplegia actually have a fulminant form of PCB.

Table 1 shows several PCB cases and our diagnosis based on the clinical features.^{1, 3-5, 9-14} Patient 2 reported by Capasso et al¹⁴ presented with ataxia in the absence of ophthalmoplegia, indicating a diagnosis of PCB overlap with acute ataxic neuropathy, an incomplete form of FS, which has been proposed elsewhere.¹⁵

Incomplete forms of PCB in patients who fail to develop both oropharyngeal and cervicobrachial weakness have been described. One such patient with confirmed *C jejuni* diarrhoea subsequently developed acute dysphagia and nasal speech in the absence of any other cranial neuropathy or limb involvement.¹⁶ Three patients with oropharyngeal palsy associated with limb ataxia but in the absence of ophthalmoplegia or limb weakness have also been described.¹⁷ There is a single report of isolated cervicobrachial weakness without pharyngeal palsy.¹⁸

PATHOPHYSIOLOGY Anti-GT1a antibodies

The immune mechanisms and neurophysiological features among GBS variants have been studied extensively and provide

useful insights into phenotypic differences. Autoantibodies against specific neuronal gangliosides have been implicated in the pathogenesis of different GBS variants. IgG anti-GM1 and anti-GD1a antibodies are associated with AMAN, but not AIDP.¹⁹ In contrast, IgG anti-GQ1b antibodies are associated with FS and BBE, both of which are characterised by ophthalmoplegia and ataxia.¹⁵ The strongest association for PCB is the presence of IgG anti-GT1a antibodies, which are discussed below.

Evidence for this first came with the identification of IgG anti-GT1a and anti-GD1a antibodies in a patient with PCB weakness associated with mild leg weakness.⁹ In contrast to anti-GQ1b antibodies detected in patients with FS and BBE, which always cross-react with GT1a,²⁰ anti-GT1a antibodies in this patient were monospecific and did not cross-react with GQ1b or GD1a. The authors postulated that since anti-GD1a antibodies had already been described in patients with AMAN,²¹ monospecific anti-GT1a antibodies might be restricted to their patient with PCB weakness. A few years later, this hypothesis was strengthened by the report of a second patient with typical PCB who showed no leg weakness and carried monospecific anti-GT1a antibodies.¹⁰ A further five patients with monospecific anti-GT1a antibodies who developed prominent oropharyngeal and neck weakness were also identified.²²

With the publication of the largest clinico-serological study of 100 PCB patients,² the significance of monospecific anti-GT1a antibodies in PCB, which had been the main focus of many investigators, was questioned. Of the 100 PCB patients, a half carried IgG anti-GT1a antibodies, which often cross-reacted with GQ1b. Furthermore, a quarter displayed IgG antibodies against GM1 or GD1a, which are often seen in AMAN.¹⁹ The overlap of serological profiles demonstrated in this study reinforces the view that GBS forms a clinical continuum and that PCB is related to FS, BBE and AMAN.

Determining why patients with anti-GT1a antibodies develop PCB is only partially understood but likely to reflect the pattern on GT1a expression within the nervous system. This assumption is based on the fact that monoclonal anti-GQ1b antibody which cross-reacts with GT1a has restricted binding to human trochlear, oculomotor and abducens nerves, while sparing the rest of the nervous system.²⁰ Given the PCB phenotype, one might predict that GT1a is concentrated in peripheral nerves innervating oropharyngeal and cervicobrachial musculature. An immunohistochemical study showed that GT1a was much more strongly expressed in the human glossopharyngeal and vagal nerves than GQ1b, whereas GQ1b and GT1a were similarly expressed in the oculomotor nerves.²²

The pattern of neuromuscular weakness in patients with botulism closely resembles that seen in FS and PCB, suggesting a shared molecular target within the nervous system. This association is supported by the observation that carbohydrate residues on gangliosides serve as receptors for botulinum toxins in neuromuscular junctions.²³ Botulinum toxin type A, the commonest cause of foodborne botulism, binds to gangliosides with varying affinity (GT1b >> GQ1b >> GD1a > GT1a > GM1) and probably disrupts the same populations of neurones.²⁴ Botulinum toxin type E also binds to GT1b, GQ1b, GT1a and GD1a.²⁵ Binding of neurotoxin to GQ1b, GT1a and GD1a may therefore explain the distribution of extraocular, oropharyngeal, cervicobrachial and leg weakness seen in botulism. Moreover, this further supports the pathogenic role of anti-GT1a or anti-GQ1b antibodies in PCB.

Demyelinating or axonal pathology

There are no postmortem or clinico-pathological correlates of PCB but detailed serial nerve conduction studies indicate a

localised pattern of neuronal damage similar to AMAN. In his original series, Ropper concluded that PCB was a regional variant of GBS supported by nerve conduction studies in the two patients as described above.¹ Notably, there were no apparent demyelinating features. In a later study, two patients with PCB weakness, one displaying antibodies against GD1a and the second against GM1b, both had axonal conduction failure consistent with AMAN.⁴ Similarly, one patient with antibodies against GT1a and GD1a and another against GT1a and GM1 also displayed reduced sensory and motor amplitudes.¹⁴ Follow-up testing in these patients showed rapid recovery in the absence of temporal dispersion, indicating no evidence of remyelination. A similar pattern was observed in a patient diagnosed with PCB overlap with FS, who displayed antibodies against GT1a and GQ1b.⁵ Together, these studies provide serological and neurophysiological evidence that PCB and AMAN form a continuum.

Several studies support the presence of molecular mimicry between gangliosides and microbial lipo-oligosaccharides in GBS. *C jejuni* isolate from a patient with acute oropharyngeal palsy, an incomplete form of PCB, expressed a GT1a/GQ1b epitope.²⁶ Applying this model, micro-organisms carrying the GT1a/GQ1b epitope could induce production of IgG anti-GT1a antibodies, with or without GQ1b reactivity, which then bound to nodal axolemma or neuromuscular junctions of peripheral nerves innervating oropharyngeal and cervicobrachial musculature. Autoantibody binding could result in complement activation followed by the disappearance of voltage-gated sodium channel clusters and the disruption of axo-glial or neuromuscular junctions, as demonstrated in animal models of AMAN,^{27, 28} and cause PCB. Immune mediated attack to the axolemma at the nodes of Ranvier may also explain reversible conduction slowing or block in some patients with PCB.^{5, 14}

A REAPPRAISAL OF CURRENT DIAGNOSTIC CRITERIA

Following his original description of PCB,¹ Ropper *et al*⁶ suggested diagnostic criteria which have not been modified and do not take account of serological data or PCB overlap syndromes. In order to recognise these additional features, we present new diagnostic criteria (box 1) based on our previous nosological classification of PCB² and those already outlined for GBS and FS.²⁹

Similar to Ropper and coworkers,⁶ we define patients who present with oropharyngeal weakness, arm weakness and arm areflexia as having typical PCB. However, in contrast to the original criteria that state that patients should have 'minimal or no paraesthesias or sensory loss' and 'normal (or virtually normal) leg power and tendon reflexes',⁶ this is not always the case.² Sensory symptoms in the upper limbs are permitted and while lower limb weakness is not a feature of 'pure' PCB, it may also be present in variable degrees, although should never be more prominent than oropharyngeal, neck and upper limb weakness. As discussed above, patients with additional features are defined as having overlap with FS or BBE and preservation of reflexes should be considered a variant of typical PCB.⁷ The clinical course should be acute and monophasic. The presence of antecedent illness, CSF albuminocytological dissociation, neurophysiological evidence of neuropathy, and detection of IgG anti-GT1a or anti-GQ1b antibodies support the diagnosis of PCB but are not essential. Other conditions, including brainstem ischaemia, myasthenia gravis and botulism should be excluded and are discussed in more detail below.

DIAGNOSTIC WORK-UP

The diagnosis of PCB can be challenging in early disease but appreciation of typical clinical features narrows the differential

Box 1 Diagnostic criteria for the pharyngeal-cervical-brachial (PCB) variant of Guillain-Barré syndrome (GBS)

Features required for diagnosis

- ▶ Relatively symmetric oropharyngeal weakness AND neck weakness AND arm weakness AND arm areflexia/hyporeflexia*
- ▶ Absence of ataxia AND disturbed consciousness AND prominent leg weakness†
- ▶ Monophasic illness pattern AND interval between onset and nadir of oropharyngeal or arm weakness between 12 h and 28 days AND subsequent clinical plateau
- ▶ Absence of identified alternative diagnosis‡

Features strongly supportive of the diagnosis

- ▶ Antecedent infectious symptoms§
- ▶ Cerebrospinal fluid albuminocytological dissociation¶
- ▶ Neurophysiological evidence of neuropathy
- ▶ Presence of IgG anti-GT1a or anti-GQ1b antibodies

*The clinical severity of each component may vary from partial to complete.

†The presence of additional features indicates overlap with other GBS variants as follows: ataxia AND ophthalmoplegia, 'PCB overlap with Fisher syndrome'; ataxia WITHOUT ophthalmoplegia, 'PCB overlap with acute ataxic neuropathy'; ataxia AND ophthalmoplegia AND disturbed consciousness, 'PCB overlap with BBE'. Leg weakness may vary considerable but oropharyngeal, neck and arm weakness should be more prominent. The absence of certain features indicates incomplete PCB as follows: upper limb weakness, 'acute oropharyngeal palsy'; pharyngeal palsy, 'acute cervicobrachial weakness (without pharyngeal palsy)'.

‡Including, but not limited to, brainstem ischaemia, myasthenia gravis and botulism.

§The presence of upper respiratory infectious symptoms or diarrhoea 3 days to 6 weeks before the onset of neurological symptoms.

¶Cerebrospinal fluid with total white cell count <50 cells/μL and protein above the normal laboratory range.

significantly (table 2). History of antecedent respiratory tract infection or diarrhoeal illness is common in GBS and often overlooked. Rate of disease progression also provides clues and is typically acute with steady progression. Brainstem ischaemia should be considered if symptoms start abruptly, while fluctuations in weakness or obvious fatigability are more suggestive of myasthenia gravis. In particular, PCB should be differentiated from myasthenic patients who display early or prominent ocular-bulbar weakness, which may be associated with antimyosin specific tyrosine kinase (anti-MuSK) and/or rarely antilow density lipoprotein receptor-related protein 4 (LRP4) antibodies in the absence of antiacetylcholine receptor (anti-AChR) antibodies. Invariably patients undergo brain imaging early that helps to exclude ischaemia, tumours or inflammatory processes. Progressive weakness is usually symmetrical and in the majority of cases (>90%) deep tendon reflexes are absent or diminished at some stage of disease. Although patients may deny sensory disturbance, it is sometimes apparent following careful examination or revealed with serial neurophysiological testing. Myasthenia gravis, botulism and other myopathic processes can usually be excluded in the presence of sensory deficits or absent reflexes.

The most important early investigation is brain MRI to exclude brainstem ischaemia, inflammation or brain tumours, which may also involve the skull base or meninges. MRI brain is normal in PCB. Blood tests are unhelpful, except for antigan-glioside antibodies (see later) although serum creatine kinase, erythrocyte sedimentation rate and C reactive protein can be deranged in inflammatory myopathies. Anti-AChR, anti-MuSK and anti-LRP4 antibody measurement are unnecessary if clinical or electrophysiological features are not consistent with myasthenia gravis. Anti-GT1a or anti-GQ1b antibody testing supports diagnosis, but is not essential.²

Normal CSF and neurophysiological testing do not exclude PCB in early disease. CSF albuminocytological dissociation is common to all GBS variants but may not be evident in 50% of patients within the first week of disease.³⁰ In the largest PCB series, CSF was abnormal in 40% of cases,² and although supportive is not essential for diagnosis. CSF cytology to exclude carcinomatous or lymphomatous meningitis is sometimes useful.

Table 2 Differential diagnosis of the pharyngeal-cervical-brachial variant of Guillain-Barré syndrome based on clinical findings

	Pharyngeal-cervical-brachial variant of Guillain-Barré syndrome	Botulism	Myasthenia gravis	Brainstem stroke
Onset	Hours	Hours	Typically with exertion	Seconds to minutes
Progression	Gradual	Gradual / descending	Fluctuating / fatiguable	Rapid / stepwise
Pattern of weakness				
Ptosis	+ / -	++	+ / -	+ / -
Internal ophthalmoplegia	+ / -	++	-	+ / -
External ophthalmoplegia	+ / -	++	+ / -	+ / -
Facial	+ / -	++	+ / -	+ / -
Bulbar	++	++	+ / -	+ / -
Arm	++	++	+ / -	+ / -
Leg	-*	++	+ / -	+ / -
Symmetrical	Yes	Yes	Variable	Variable
Hypo / areflexia	+++	-	-	-
Sensory deficit	+ / -	-	-	+ / -
Other clinical features	Antecedent infectious symptoms	Dry mouth, dizziness, and gastrointestinal symptoms.		

++, present; +/-, sometimes present; -, not present.

*Leg weakness can be mild. **10% of patients have normal or exaggerated reflexes.

Detailed neurophysiological work-up can be valuable, especially in the absence of sensory symptoms. Low and high frequency repetitive nerve stimulation can be used to assess patients with myasthenia gravis and botulism respectively. Single fibre electromyography is abnormal in patients with myasthenia gravis and botulism.³¹ It is important to note, however, that as single fibre electromyography appears to be normal in limb muscles in patients with FS, AMAN and AIDP,^{32, 33} it might therefore also be expected to be normal in PCB. The usefulness of median nerve somatosensory evoked potentials and cervical root stimulation when assessing patients with PCB remains unknown. The neurophysiological findings in PCB are axonal rather than demyelinating. Repeat testing after a few days is advised if initially normal, which may be the case in early disease.

The following case highlights the importance of recognising PCB early in order to avoid unnecessary investigations and inappropriate treatment.

CASE HISTORY

An elderly patient presented to the emergency department in our institution with a 1-day history of progressive speech disturbance, swallowing difficulty, upper limb weakness and ptosis. They denied any sensory deficit and neurological examination revealed normal deep tendon reflexes. They were initially diagnosed by the admitting doctor as having myasthenia gravis, although brainstem ischaemia was also considered and they went on to have a CT brain with contrast, which was normal. Careful examination by the neurology team the following morning revealed additional subtle sensory disturbance in both upper limbs, which together with bulbar, neck and proximal upper limb weakness prompted a diagnosis of PCB. This was supported by recognition of an antecedent upper respiratory tract infection 1 week previously. Plasma exchange was initiated immediately. They were intubated on day 2 due to severe bulbar dysfunction and retention of carbon dioxide. Upper limb strength and sensory loss slowly progressed and peaked on day 10 at which point power was Medical Research Council (MRC) grade 1 proximally and 0 distally. Nerve conduction studies on day 1 only showed slight reduction in sensory amplitudes in the upper limbs. By day 7 there was marked reduction in motor amplitudes in the face and upper limbs and to a lesser extent in the lower limbs. CSF revealed normal protein level and no inflammatory cells on day 7. Our final diagnosis was PCB and was confirmed by the presence of anti-GT1a-, anti-GQ1b and anti-GD1b antibodies.

TREATMENT

The general principles of GBS management and immunotherapy, including the use of intravenous immunoglobulin or plasma exchange, have been reviewed elsewhere,³⁴ but some features of PCB are worthy of discussion. Prompt diagnosis of PCB and exclusion of other treatable causes should be carried out while in hospital, rather than the out-patient setting as bulbar weakness may develop rapidly. Ongoing assessment of bulbar function and respiratory effort is mandatory and guides the respective use of nasogastric feeding and ventilator support. In the largest series, patients with pure PCB were more likely to require intubation than those with overlap syndromes and this correlated with degree of bulbar involvement.²

SUMMARY

PCB is probably less rare than previously thought, yet its phenotype remains unfamiliar to many neurologists and general physicians. Diagnosis can be made on history and neurological findings alone and helps differentiate it from other causes of

oropharyngeal and cervicobrachial weakness. Knowledge that PCB forms a clinico-pathological continuum with FS in many ways is the most important take-home message from this review and explains its varied presentation and misdiagnosis.

Acknowledgements We are grateful to Dr Nortina Shahrizaila (University of Malaya) and Professor Einar Wilder-Smith (University of Singapore) for their suggestions and critical reading of the manuscript.

Contributors Study concept and design: BRW and NY; drafting of the manuscript: BRW and NY; critical revision of the manuscript for important intellectual content: NY; study supervision: NY.

Funding This study was supported by the National Medical Research Council (IRG 10nov086 to NY) in Singapore.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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