September 2017, one case of hyperinsulinism and two endocrine-related cases were identified. The increased availability of FFA-to-3OHB ratios allowed more targeted differential diagnoses of paediatric hypoglycaemia.^{3,4} Of note, the percentage 'success' increased from 68% to 95% for plasma ammonia, from 64% to 88% for plasma amino acids and from 46% to 86% for blood spot acylcarnitine/amino acid profiles before and after the introduction of the new hypopack (Table 2).

Conversations with clinicians revealed some potential causes for the lower percentage successes of hypoglycaemia screens prior to introduction of the new hypopack. Some clinicians had the false impression that a Guthrie card (dried blood spots) was solely for newborn screening and were not aware that the sample type was also used for acylcarnitine/amino acid profile, therefore Guthrie card samples might have been omitted if the blood samples had to be prioritised. Raised plasma ammonia in the context of hypoglycaemia may assist with differential diagnoses such as organic acid-aemias and fatty acid oxidation disorders. However, some clinicians assumed that plasma ammonia measurement was only useful in the setting of liver disease and this might explain the missing of plasma ammonia from some hypoglycaemia screens. Hence, education of clinicians and introduction of the new hypopack (evidence-based and with joint input from clinicians and laboratory specialists) may ensure that essential pathology samples are collected at all acute hypoglycaemic events. There appeared to be a large increase in hypoglycaemia episodes from 39% (January 2013–December 2014) to 60% (January 2016–December 2017) found in this audit. One possible explanation (and limitation of this audit) is the use of arbitrary inclusion criteria which may result in some true hypoglycaemia sample sets being excluded from the audit because they had neither a pathology request form with 'hypoglycaemia' written on the form nor a unique hypopack sheet accompanying the samples.

The new hypopack introduced at the Monash Children's Hospital has revolutionised paediatric hypoglycaemia screens, most notably improving the number of appropriately performed investigations (reducing unnecessary investigations) and allowing these tests to be performed with limited blood volumes in a timely manner. The ongoing success of this pack depends on close collaboration between clinicians and laboratory specialists including ongoing clinician education, especially with regular rotation of junior staff.^{1,2}

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An unexpected diagnosis: leukaemic presentation of blastic plasmacytoid dendritic cell neoplasm with massive splenomegaly

Sir,

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and aggressive haematological malignancy. In the case reported here, it presented unusually, with painful massive splenomegaly.

A 67-year-old man presented with a 2-week history of left sided abdominal pain. He had a history of renal calculi, but no other past medical history. Physical examination demonstrated massive splenomegaly and inguinal and supraclavicular lymphadenopathy. There were occasional small bruise-like lesions. The peripheral blood count demonstrated a moderate thrombocytopenia ($44 \times 10^9/L$), but otherwise normal parameters (haemoglobin 144 g/L, white cell count $6.0 \times 10^9/L$). The blood film was leukoerythroblastic with occasional abnormal circulating cells (Fig. 1A).

Bone marrow aspirate demonstrated a markedly hypercellular marrow with preserved megakaryopoiesis, reduced myeloid and erythropoiesis with an extensive infiltrate (85% of nucleated cells) of intermediate-to-large sized abnormal cells. These cells displayed blastic morphology, basophilic cytoplasm with pseudopod-like extensions, cytoplasmic fragments and occasional cytoplasmic vacuoles (Fig. 1B).

Flow cytometry identified a population of cells in the blast-gate (i.e., dim CD45) expressing CD4, CD56, CD123, variable CD117 but not CD34, confirming the diagnosis of blastic plasmacytoid dendritic cell neoplasm. Of note, CD117 immunohistochemistry was negative on the trephine. Cytogenetics demonstrated a complex karyotype with loss of chromosomes 13 and 21 and additional material of unknown origin on 1p, 12p and 22p.

Splenectomy was performed because of splenic haemorrhage and a subtle, bruise-like skin lesion was biopsied concurrently. The spleen weighed 2390 g. The splenic and skin histopathology was consistent with BPDCN.

Cerebrospinal fluid cytology and flow cytometry also demonstrated central nervous system (CNS) involvement.

BPDCN is a rare, aggressive, haematological malignancy without clearly defined incidence or clearly understood aetiology.¹ It was initially described in 1995 as a group of CD4+ CD56+ malignancies initially called blastic natural killer lymphoma/leukaemia.^{2,3}

Skin lesions are the first manifestation that typically result in medical attention.^{1,3,4} These skin lesions are brown to violaceous, solitary through to multiple nodules, plaques or bruise-like lesions.⁴ Lymphadenopathy at presentation is common, reported in 20–50% of cases.^{1,3,4} Ultimately, peripheral blood and bone marrow involvement ensue.¹ A minority of cases

Fig. 1 (A) Blood film with occasional abnormal circulating cells (Wright stain). (B) Bone marrow aspirate with intermediate-to-large sized abnormal cells which displayed blastic morphology, basophilic cytoplasm with pseudopod-like extensions, cytoplasmic fragments and occasional cytoplasmic vacuoles (Wright stain).

(less than 20%) may present with a leukaemia, with only isolated bone marrow and peripheral blood involvement.^{3,5} Up to 25% of cases with skin disease may also have a concurrent leukaemic component. CNS involvement also occurs relatively frequently at diagnosis (5–10%) and possibly more frequently at the time of relapse.^{3,4,6}

Since most patients present with skin disease, the diagnosis is typically made via histology; however, as in the case presented, a minority of patients will have no, or only subtle, skin changes. This means that some patients will require a diagnosis based on peripheral blood and bone marrow analysis. Such cases can be diagnostically challenging. One series of BPDCN described 23 cases with bone marrow involvement and described detailed morphological findings in peripheral blood and bone marrow.³ The malignant cells are variably sized (from small to large) with large volume, lightly basophilic, agranular cytoplasm. Cytoplasmic vacuolation is common, typically occurring at the cytoplasmic margin with variably sized vacuoles, and cytoplasmic pseudopodia-shaped expansions may also be seen. Variable nuclear characteristics include a regularly shaped nucleus in 56% of cases, and irregular (notched, folded or bilobed) in the remainder of cases. Chromatin patterns were noted to be intermediate in 56% of cases and fine or lacy in the remainder.³

Despite the detailed morphological description, diagnosis of BPDCN relies heavily on the peripheral blood or bone marrow immunophenotype. The flow cytometry immunophenotype of BPDCN is best characterised as a neoplasm that does not express lineage-specific antigens, but expresses CD4, CD56, CD45RA (dim) and plasmacytoid dendritic cell-associated antigens: CD123 (bright expression), BDCA-2/CD303, TCL1A and CD2AP.⁵ The absence of CD4 or CD56 does not exclude the diagnosis as long as there are plasmacytoid dendritic cell-associated antigens present, and may occur in up to 8% of cases.¹

There are no specific karyotypic abnormalities, although complex karyotypes are frequently reported. The karyotype is abnormal in 66% of cases and there are six recurrent abnormalities recognised involving: 5q21 and 5q34, 12p13, 13q13-21, 6q23, 15q and loss of chromosome 9.¹

The cell of origin is a haematopoietic stem cell and the normal counterpart is the precursor of plasmacytoid dendritic cells.¹

The most unusual feature of this case is the presentation with painful, massive splenomegaly. Two case series with

more than 20 cases report splenomegaly in 35–40% of cases.^{3,6} However, splenomegaly was not reported on in the largest series of 90 patients.⁴ Additionally, there do not appear to be any reports of BPDCN presenting with massive splenomegaly.

It is also interesting to note a significant degree of discordance between the peripheral blood morphology and the bone marrow morphology of the BPDCN cells. The BPDCN cells in the bone marrow frequently had elongated forms with ragged cytoplasmic margins, blebbing and disintegrating fragments (Fig. 1B). These findings were not present in the peripheral blood. This compounds the challenging nature of the diagnostic process in the absence of characteristic skin lesions. There are reports in the literature of misdiagnoses on the basis of blood film examination where flow cytometry has not been performed.⁷

Additionally, this case highlights the importance of a carefully selected flow cytometry panel that will identify BPDCN in leukaemic phase, or with bone marrow involvement and minimal skin involvement. This requires CD123 (or other plasmacytoid dendritic cell-associated antigen) antibodies in a standard acute leukaemia screening panel. If such antibodies are not part of the routine antibody cocktail, the detection of a neoplasm that dimly expresses CD45, and is positive for CD4 and CD56, without additional lineage-specific marker, must result in a reflex addition of an antibody to a plasmacytoid dendritic cell-associated antigen.

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The delayed diagnosis of myeloproliferative neoplasms is common and results in a high incidence of potentially preventable thrombotic complications

Sir,

There is a high incidence of thrombotic complications in patients with myeloproliferative neoplasms (MPN) prior to or at the time of diagnosis which reduces their quality of life and increases their risk of recurrent thrombotic events. We performed a retrospective chart review to determine the duration of blood count abnormalities prior to diagnosis and the incidence of potentially preventable thrombotic and haemorrhagic complications occurring during this time. In 147 patients included in this audit we found a significant delay from the appearance of MPN-associated blood count abnormalities until the diagnosis of a MPN was established. During this time 25% of the patients had a potentially preventable thrombotic or haemorrhagic event.

The Philadelphia (Ph)-negative myeloproliferative neoplasms (MPN) are a heterogeneous group of bone marrow disorders characterised by haematopoietic cellular proliferation with the excess production of mature blood cells resulting in characteristic anomalies in the peripheral blood.

Patients with these disorders are at increased risk of thrombotic and haemorrhagic complications, which contribute to morbidity and mortality, have an adverse impact on quality of life and are predictive of future thrombotic events.^{1,2} Thromboembolic events are reported to have occurred at or prior to diagnosis in 12–39% of polycythaemia vera (PV), 11–25% of essential thrombocythaemia (ET) and 13.2% of primary myelofibrosis (PMF) patients.^{2,3} The frequency of thrombosis has been consistently reported to be greater than that of bleeding and those occurring at the time of diagnosis have traditionally been assumed to be unpreventable. We performed an audit of our MPN patients to determine the duration of blood count abnormalities prior to diagnosis and the incidence of potentially preventable thrombotic and haemorrhagic complications occurring during this time.

All adult patients diagnosed with a Ph-negative MPN [ET, PV, PMF or myeloproliferative neoplasm-unclassifiable (MPN-U)] between January 2010 and June 2017 under the care of haematologists at our centre were included in the audit. The blood count results of each patient were obtained and the date of the first appearance of a MPN-associated blood count abnormality was recorded. These included persistent polycythaemia, leukocytosis or thrombocytosis, or a leukoerythroblastic blood film. The hospital and specialist medical records of each patient were reviewed and the dates of any adverse thrombotic or haemorrhagic events potentially attributable to a MPN were identified. The time between the first blood count abnormality on record and diagnosis was recorded as diagnostic delay. All data were tabulated in a de-identified database and statistical analysis was performed.

The major results of the audit are summarised in Table 1. A total of 147 patients with a new diagnosis of a MPN were identified, including 37 patients with PV, 71 patients with ET, 26 patients with PMF and 13 patients with MPN-U.

The 37 patients with PV were all positive for JAK2V617F and had a mean age of 73 years (range 47–92 years). The median diagnostic delay was 456 days (range 0–2650 days). During this time 10 of the 37 patients (27%) had potentially preventable complications: nine patients had thrombotic events which consisted of arterial events in seven patients (5 cerebrovascular, 2 cardiac events) and venous thrombosis in two patients, and one patient had a haemorrhagic event.

Of the 71 patients with ET, 63% were positive for JAKV617F mutation, 14% were positive for a CALR mutation, 1.4% had a MPL mutation, 8.5% were triple-negative, and 12.7% were JAK2V617F negative but had no further

Table 1 Diagnosis delay and incidence of potentially preventable thrombotic and haemorrhagic complications

Diagnosis	No. patients	Median diagnosis delay, days (range)	Number of patients with events			
			Total	Thrombotic		Haemorrhagic
				Arterial	Venous	
Total	142	723 (0–8731)	36 (25%)	22 (15.5%)	12 (8.5%)	4 (2.8%)
PV	37	457 (0–2650)	10 (27%)	7 (18.9%)	2 (5.5%)	1 (2.7%)
ET	71	825 (0–8731)	18 (25%)	13 (18.3%)	5 (7%)	—
PMF	26	256.5 (0–3684)	4 (15%)	1 (3.8%)	3 (11.5%)	—
MPN-U	13	1371 (442–3244)	4 (31%)	1 (7.7%)	2 (15.4%)	3 (23.1%)

ET, essential thrombocythaemia; MPN-U, myeloproliferative neoplasm-unclassifiable; PMF, primary myelofibrosis; PV, polycythaemia vera.