INTRODUCTION

Melanoma is a leading cause of morbidity and mortality in young Australians.\(^1\) It is also one of the most common cancer diagnoses made during pregnancy or the peripartum period.\(^2\) Transcoelomic abdominal metastasis of melanoma, usually widespread, is not uncommon; however, isolated metastasis to the gallbladder is unique and described in fewer than twenty cases in the literature.\(^3\)--\(^5\)

This article presents the case of a 34-year-old woman presenting with biliary symptoms eight months postpartum. The patient underwent investigations which identified a mass in the gallbladder lumen. A mini-laparoscopic cholecystectomy was performed, and histology of the mass was consistent with metastatic melanoma. No further sites of metastasis were identified. The patient had a history of an early cutaneous melanoma 29 months prior to this presentation, which had been excised with acceptable margins. Following her cholecystectomy, she received adjuvant immunotherapy as a part of a clinical trial. At the time of writing, the patient remains alive with no melanoma recurrence at 42 months postcholecystectomy.

The development of solitary gallbladder metastasis in melanoma is highly unusual, and the pathogenesis of why this may occur is still unknown due to the paucity of literature describing this. None of the previously documented cases of isolated gallbladder metastasis in melanoma have been in a woman in the months post-partum, nor have they occurred following such an early primary lesion, making this a unique case.

Melanoma is the third leading cancer diagnosis in Australia and is a particularly important cause of cancer-related morbidity and mortality in young adults.\(^1\) Primary melanoma in pregnancy is also increasingly described.
in the literature and poses many challenges in diagnosis and management.\textsuperscript{2,6,7} Despite its high prevalence, we continue to see atypical and novel presentations of metastatic melanoma. These are notoriously difficult to diagnose, and many unusual sites of metastasis are identified post-mortem.\textsuperscript{8}

Solitary metastasis to the gallbladder from any source is a rare phenomenon.\textsuperscript{3–5} Of these, melanoma was identified as the primary cancer in 50%–67\% of cases.\textsuperscript{4} Diagnosis is often difficult, with many patients completely asymptomatic or occasionally presenting with biliary symptoms.\textsuperscript{9}

The case described here is novel in a number of ways: The patient had a very early primary lesion, she is one of fewer than twenty cases of isolated gallbladder metastasis found in the literature and to the best of our knowledge is the first case occurring just months post-partum.\textsuperscript{3–5}

2 | CASE PRESENTATION

A 34-year-old woman presented to the emergency department of a regional hospital with acute epigastric pain radiating to her back following a meal. She recalled one previous episode during her first pregnancy 5 years prior, which had never recurred and had therefore never been investigated. She had not had any recurrence of symptoms even with her two more recent pregnancies, the last being only eight months prior to this presentation. On examination in the emergency department, she appeared well and had vital signs within normal limits. Her abdomen was soft with no focal tenderness. She was found to have deranged liver function tests (bilirubin of 13 umol/L, ALT 261 U/L, AST 623 U/L, ALP 215 U/L, and GGT 168 U/L) and normal inflammatory markers (white cell count and C reactive protein). Her pain resolved over the course of several hours, and she was presumptively diagnosed with biliary colic. She was managed with simple analgesia only (paracetamol and ibuprofen) and was discharged from the department with a referral for an outpatient hepatobiliary ultrasound.

Her ultrasound 3 days later unexpectedly demonstrated a 58 × 23 × 20 mm, heterogenous soft tissue lesion with some vascularity, in keeping with gallbladder adenoma or polyp. She was referred to a surgeon, who organized an MRCP to further assess the mass, which was performed 2 weeks later. This demonstrated a subtly enhancing mass, nearly filling the entirety of the gallbladder lumen (Figure 1). There was no extension outside the gallbladder wall, and the adjacent liver was normal. There was no intrahepatic or extrahepatic duct dilatation. At this time with the clinical picture and imaging findings, the leading differential was a gallbladder adenoma. She was booked for a laparoscopic cholecystectomy the following week.

A mini-laparoscopic three port cholecystectomy (Hasson 12 mm port and two mini-laparoscopic 5 mm ports) was performed, taking great care to preserve the cystic node with the gallbladder specimen and to keep the gallbladder wall intact (Figure 2). The gallbladder was not inflamed, and there was no evidence of gallbladder fossa invasion. The gallbladder was retrieved within a retrieval bag and was delivered without resistance through the neck of an umbilical hernia which was used for Hasson port entry and which was repaired at the end of the operation. The specimen was confirmed intact and, when opened, revealed a large fleshy and friable soft tissue mass occupying the lumen (Figure 3). The mass had been intact upon opening but fragmented before the pathologist reported on it (Figure 4).

The patient recovered well and had no complications. She was discharged on day 1 post-operatively.

Histological examination of the gallbladder mass was consistent with malignant melanoma having the following immunohistological features: S100+, SOX10+, MelanA+, HMB45+, AE1/AE3-, and CAM5.2-. In areas, the tumor cell cytoplasm contained brown pigment in keeping with melanin. Where the mass was connected to the gallbladder mucosa, it was reported to have polypoid architecture. There was no invasion beyond the mucosa, and no lymphovascular or perineural invasion. Foci of necrotic tumor were noted (Figure 5). The cystic duct lymph node showed benign, reactive changes with no metastatic deposits.

The gallbladder wall was found to be mildly thickened with scattered chronic inflammatory cells and some neutrophils, reported as mild acute on chronic cholecystitis.

On review of the patient’s past medical history, it was found that she had undergone excision of a pigmented lesion on her right posterior neck 29 months prior, which
was found to be a malignant melanoma arising on one side of a benign nevus. This was non-ulcerated, had a Breslow thickness of 0.6 mm, Clark level II, with no mitoses observed, no microsatellites, and no lymphovascular invasion. There was an adjacent component of superficial spreading type melanoma. The closest margin at initial incision was 2 mm. A wide excision was performed by a surgeon with no residual tumor found. She was classified as Stage IA melanoma, and therefore at low risk of recurrence (less than 5%). She was referred to a dermatologist for ongoing surveillance.

Following her new diagnosis of metastatic melanoma of the gallbladder, the patient underwent staging PET-CT of the chest, abdomen and pelvis and MRI of the brain. There was no evidence of further metastatic disease on imaging. Her dermatology review was brought forward with no concerning lesions. She was referred to an oncologist with an interest in melanoma. She went on to participate in the Checkmate 915 Adjuvant Immunotherapy Trial with Nivolumab/Ipllimumab (combined vs. monotherapy) but had to withdraw after 9 months of therapy subsequent to immune-related adverse events (autoimmune pancreatitis). The intended duration of her therapy had been 12 months. Nivolumab and Ipllimumab are both agents used in the current recommended regime for adjuvant immunotherapy in metastatic melanoma. Fortunately, at the time of writing, the patient has remained alive with no evidence of melanoma relapse at 42 months postcholecystectomy.
To identify previous cases, a search was conducted over multiple research databases (PubMed, Cochrane Library, and JAMA Network) using key phrases including “melanoma,” “gallbladder metastasis,” and “gastrointestinal metastasis”. Additionally, the same databases were used to search for “melanoma in pregnancy” and “gallbladder metastasis.” The stated number of fifteen previous cases of solitary gallbladder metastasis in melanoma is based on the documented cases found on these databases, both documented as individual case reports and listed as a part of previous systematic reviews.

3 | SEARCH METHODS

4 | DISCUSSION

Australia has the highest incidence of melanoma in the world, with this being the most common cancer affecting the 15- to 39-year-old age group.1 This case, however, is unique in several ways. Notably, the presence of a solitary gallbladder metastatic deposit with no other distant metastases is a rare phenomenon with few reports in the literature. The primary lesion was of a very early stage; however, it was excised from the neck which does increase the risk of relapse compared to a peripheral location.4 The Nomogram reported by Verver et al.10 would have given this patient an 8% 5-year recurrence rate (compared to 3% had the lesion been on her arm). What factors may have influenced this melanoma to metastasise specifically to the gallbladder in this patient?

Metastasis to the gallbladder, although uncommon, has been described extensively in the literature. Typically, these gallbladder metastases are part of transcoelomic metastatic disease, with the gallbladder component asymptomatic and only identified post-mortem, as distinct from hematogenous metastasis. In a retrospective study of 125 patients with metastatic melanoma who underwent post-mortem evaluation, 15% had some metastatic deposits in the gallbladder, much higher than the reported numbers in living patients. In the subset of patients who do have gallbladder metastases diagnosed in life, their prognosis is poor with a median survival of 8.4 months after diagnosis.11 There are only 15 well-documented cases of solitary gallbladder metastases from melanoma. Of these cases, the mean age of diagnosis was 53.4 (range 35–77), with none as young as the patient described here. Unfortunately, fewer than half of the documented cases included detailed histological records of the primary lesions. Of those that did, the Breslow thicknesses were in the range of 2.2–12.0 mm and all reported a Clark level of IV. It is important to note that these were all much further advanced histologically than the case presented here, with a Breslow thickness of only 0.6 mm and Clark level of II.

The documented incidence of cutaneous melanoma in pregnancy in Australia is 45 per 100,000 pregnancies.6 The case presented is currently the only documented case of solitary gallbladder melanoma metastasis in a young woman months post-partum. The influence of pregnancy on melanoma is a contentious issue, with many differing reports and opinions on risk, prognosis, and management.12 There is significant confounding data discussing whether pregnancy increases the risk of developing a primary melanoma, or of developing metastatic deposits in patients with new or previous primary cutaneous melanoma.7 While many papers have stated there is no difference in outcomes, there are certainly plausible risk factors associated with pregnancy that have been suggested as contributing factors to the development of metastatic disease. Factors postulated to increase metastasis in pregnancy include the presence of increased lymphangiogenesis, presence of increased concentrations of growth factors that may promote tumor growth, presence of PAPPA (pregnancy-associated plasma protein A) which has been implicated in the progression of melanoma in pregnant women, and finally the lowered immune state in pregnancy.2,13 Given the lack of other documented cases of gallbladder metastasis in the peri-partum period, any estimations of increased risk of gallbladder metastases are purely anecdotal at this stage. It is possible that the combination of pregnancy factors described as well as biliary stasis and gallbladder inflammation associated with pregnancy may have formed a fertile site for deposit of metastatic disease.

In conclusion, this case describes a solitary melanoma metastatic deposit to the gallbladder occurring in a woman only months post-partum, a clinical scenario which has not previously been documented in the literature. As the only case of its sort, it is not possible to draw concrete conclusions regarding possible contributing factors. There have been several possible predispositions described here that would benefit from being explored further in future case reports. We also hope that, given the positive outcome of this case to date, the management may provide some insight if similar cases occur.

CONFLICTS OF INTEREST

The authors have no competing interests to declare.

AUTHOR CONTRIBUTIONS

PG collected case information and was directly involved in patient care. ED collated patient information and formulated the review of literature, case review, and discussion. All authors were involved in reviewing the manuscript and approving the final version. The corresponding author
attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

CONSENT
The authors confirm that informed written consent was obtained from the patient in accordance with the journal’s patient consent policy.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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