



Case Report

CASE REPORT: BAP1-Inactivated Melanoma Arising in a Cellular Blue Nevus of the Cheek: A 9-Year Evolution From Incomplete Excision to pT4 Melanoma

Olav Tammik^{1*}, Terje Arak², Margus Reimann³

¹Department of Surgical Oncology and Gynecology, Clinicum of University of Tartu, 50406 Tartu, Estonia

²Department of General and Plastic Surgery, Clinicum of University of Tartu, 50406 Tartu, Estonia

³Department of Pathology, Clinicum of University of Tartu, 50406 Tartu, Estonia

*Corresponding author: Olav Tammik, Department of Surgical Oncology and Gynecology, Clinicum of University of Tartu, 50406 Tartu, Estonia

Citation: Tammik O, Arak T, Reimann M. (2026). CASE REPORT: BAP1-Inactivated Melanoma Arising in a Cellular Blue Nevus of the Cheek: A 9-Year Evolution From Incomplete Excision to pT4 Melanoma. Ann Case Report. 11: 2651. DOI: 10.29011/2574-7754.102651

Received: 05 July 2026; **Accepted:** 10 July 2026; **Published:** 13 July 2026

Abstract

Background: Cellular blue nevus (CBN) is a benign dermal melanocytic tumor that can extend deep into the dermis and subcutaneous tissue. In rare cases, melanoma may develop in association with a blue nevus. Loss of BAP1 (BRCA1-associated protein 1) is a molecular process associated with the progression of melanocytic tumors. This article highlights key observations regarding the challenges in diagnosing this rare subtype of melanoma, its histopathological features, and treatment considerations.

Case Presentation: A 36-year-old male underwent excision of two adjacent nevi on the left cheek in 2016. Histopathology demonstrated an intradermal nevus with clear margins and a cellular blue nevus without malignant features; however, margins of the cellular blue nevus were not assessable. No postoperative surveillance was arranged. Within 2-3 months after the first surgery, a small lump appeared under the skin, which has gradually but rapidly grown over the past two years. In 2025, the subcutaneous lesion measured approximately 2.5 cm. Clinically evident facial asymmetry was observed, which had not been apparent prior to the initial surgical procedure in 2016. Imaging showed a well-circumscribed vascularized subcutaneous tumor without distant metastases. Initial extirpation revealed a lobulated pigmented tumor with satellite nodules. Final histopathology demonstrated melanoma arising in association with cellular blue nevus with loss of BAP1 expression. Subsequent extensive local excision and sentinel lymph node biopsy revealed no residual tumor or lymph node metastases. A multidisciplinary oncology team decided to treat the surgical finding as a soft-tissue metastasis of melanoma and administered adjuvant systemic biological therapy to the patient for one year. The patient remains under oncological and dermatological follow-up.

Conclusion: This case illustrates the malignant transformation of a residual cellular blue nevus into a BAP1-inactivated melanoma following incomplete excision and long-term persistence. Indistinct surgical margins and/or progressive nodular growth at the site of a previous cellular blue nevus excision should raise suspicion of the possibility of malignant transformation and warrant structured follow-up, as the risk of malignant progression is rare but serious. Early detection and appropriate surgical and oncological treatment are crucial for improving patient outcomes.

Key Takeaways: Cellular blue nevi can rarely transform into melanoma. Nevi with indistinct borders require follow-up. Melanoma arising in blue nevus often shows: Deep location, nodular growth, heavy pigmentation, satellite nodules. Loss of BAP1 is a warning sign of aggressive behavior. Loss of BAP1 is a warning sign of aggressive behavior. Genetic predisposition increases the risk of malignant transformation.

Case Presentation

A 36-year-old Estonian man with no significant past medical history consulted a doctor in 2016 regarding skin changes on his left cheek. The patient reported that the skin changes had appeared about a year before he sought medical attention. There were no accompanying symptoms, such as pain, ulceration, bleeding, or rapid growth. Clinical examination revealed two pigmented skin lesions located very close to each other. The first was a 2-mm skin-colored papule consistent with a melanocytic nevus. Approximately

1 mm away from this lesion was a second 2-mm bluish papule. No regional lymphadenopathy was observed. No dermatoscopic findings were documented. Given the clinical presentation and the proximity of the two lesions, a single excision procedure was performed under local anesthesia. The intraoperative finding revealed that the 2-mm papule was the superficial, protruding portion of an 8-mm nodule located in the subcutaneous tissue. The wound was closed in two layers, and the sutures were removed seven days after surgery without complications.

Histopathological examination of the excised specimen (1.1 × 0.9 cm) demonstrated two distinct melanocytic lesions: Intradermal pigmented nevus, completely excised with histologically free margins (R0 resection) and Cellular blue nevus 8 mm in depth without clear histological features of malignancy and with involvement of excision margins (complete/R0 excision was not histologically confirmed) [1-11].

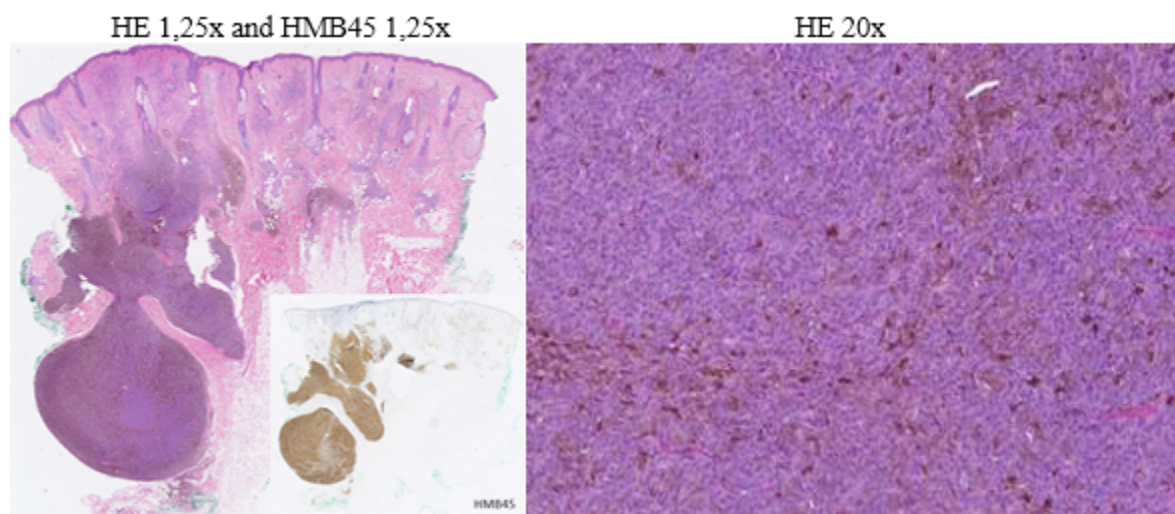


Figure 1: Histopathological findings of the primary excision in 2016.

Microscopic examination demonstrated a dermal and subcutaneous melanocytic neoplasm composed predominantly of epithelioid melanocytes arranged in solid sheets and nests. A central necrotizing nodular zone with abundant melanophages was observed. The peripheral tumor component showed highly proliferative epithelioid melanocytic cells with nuclear atypia and prominent nucleoli. Scattered spindle and dendritic melanocytes consistent with a residual blue nevus component were also identified. A histologically centrally necrotic nodule containing melanophages and, more peripherally, proliferations of predominantly epithelioid melanocytic cells (BAP1-, HMB45+) along with a few spindle-shaped melanocytic cells (likely a remnant component of a blue nevus). Immunohistochemically, the tumor is positive for S100, HMB45, melanA, and MITF. Ki67 shows low proliferative activity (5%).

Despite the uncertainty regarding margin status, no postoperative surveillance plan was established. For the following 7 years no clinical follow-up of the operative site was scheduled, and no re-excision was considered. Approximately 2-3 months following the initial excision in 2016, the patient noted the development of a small subdermal nodule beneath the operative scar. No immediate medical consultation was sought at that time.

By 2025, the lesion had been present for approximately nine years. The patient reported that the lesion had gradually enlarged over the past two years. Due to the rapid progression and worsening facial asymmetry that had developed in recent months, he consulted a general surgeon and was subsequently referred to a plastic surgeon for further evaluation. On inspection, an atrophic postoperative scar was present on the left cheek. Beneath the scar, a firm subcutaneous nodular tumor measuring approximately 2.5 cm in diameter was palpated. The lesion was movable relative to the underlying musculature. Clinically evident facial asymmetry was observed, characterized by inferior displacement of the left oral commissure and relative shortening of the left hemilip. These findings suggested possible mass effect on the mimetic musculature and/or involvement of peripheral branches of the facial nerve. As asymmetry appeared after the first operation, then previous nerve damage may be considered.

An ultrasound examination revealed a hypoechoic structure measuring 2.0×1.1 cm. A Doppler examination showed increased vascularity both within and around the lesion, suggesting a solid, vascularized soft-tissue tumor. Magnetic resonance imaging performed in May 2025 revealed a well-circumscribed tumor measuring 1.8 cm in maximal diameter. No definitive infiltration into adjacent musculature or osseous structures was described. Radiologist impression - more likely benign tumor [1-11].

Surgical Management

In September 2025, surgical extirpation of the lesion was performed under local anesthesia. Intraoperatively, a bluish-black, lobulated tumor with a thin capsule was identified in the subcutaneous tissue beneath the atrophic scar. The tumor was removed with macroscopically clear margins. In addition to the dominant lesion, several smaller nodular lesions of similar macroscopic appearance were identified in the surrounding subcutaneous tissue and were removed during the same procedure. The wound was closed in two layers with an intracutaneous suture technique. No immediate perioperative complications were reported.

Histopathological examination of the excised specimen: A round, dark purple nodule measuring 1.7 cm in diameter. The cut surface is reddish-brown with some yellowish spots.

Microscopic examination demonstrated: A nodule with central necrosis, surrounded peripherally by numerous melanophages, with scattered spindle-shaped and dendritic melanocytes (primarily representing the preserved blue pigment component), and, at the outermost periphery, predominantly atypical proliferation of epithelioid melanocytes. Immunohistochemically HMB45-positive; loss of BAP1 expression is present in the epithelioid atypical melanocytes.

Summary: Given the previous finding of cellular blue nevus and the atypical melanocytic proliferation present in this specimen, which is characterized by loss of BAP1, this is primarily a BAP1-inactivated melanoma arising from a blue nevus (a recurrence of the blue nevus has developed in the area of the previous blue nevus scar and has become malignant). Histologically blue nevus-associated melanoma with BAP1 inactivation (pT4, RX).

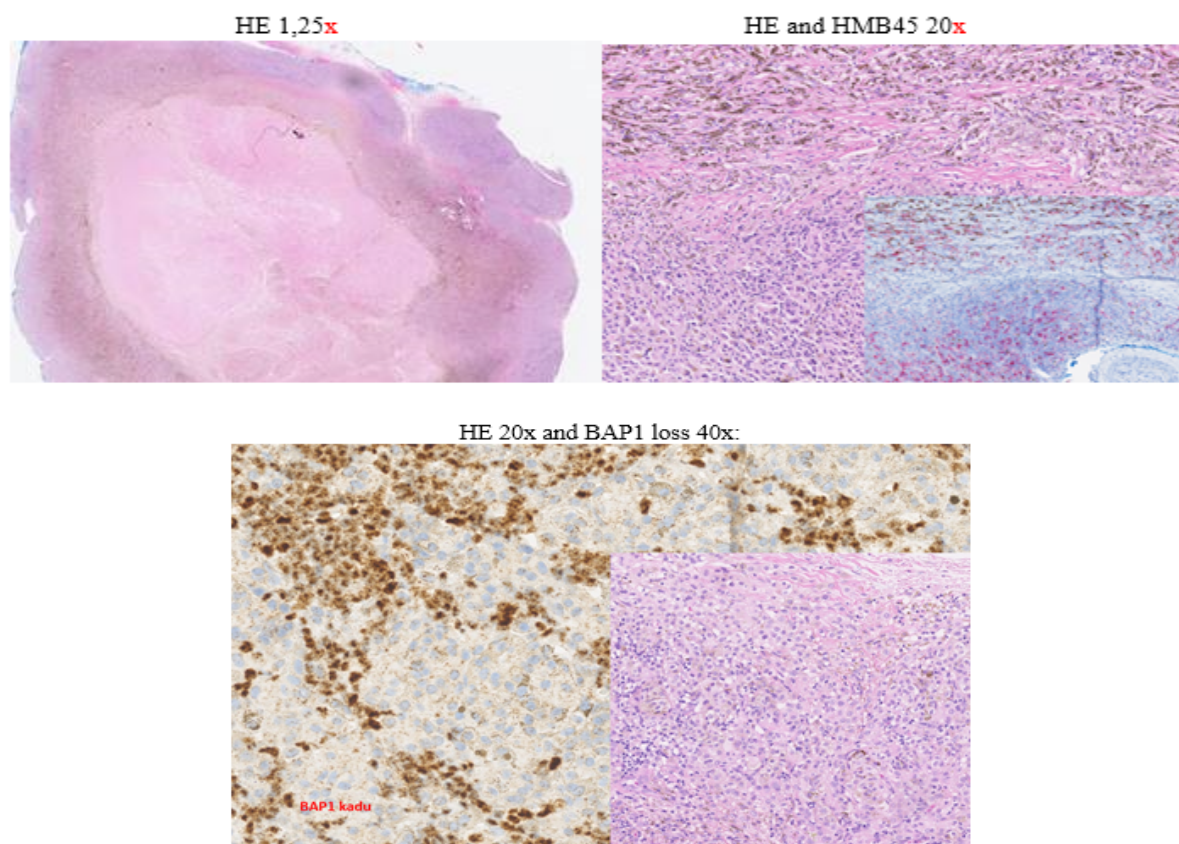


Figure 2: Histopathological findings of the recurrent lesion diagnosed in 2025.

Following histopathological evaluation of the September 2025, additional surgical intervention was indicated and preoperative whole-body positron emission tomography computed tomography (PET-CT) was planned. There was no radiologic evidence of regional lymph node involvement or distant metastatic disease attributable to the facial tumor. However, PET-CT demonstrated an incidental focus of increased fluorodeoxyglucose (FDG) uptake within the sigmoid colon. Subsequent colonoscopic resection of the sigmoid lesion was performed. Histopathological analysis revealed a **tubulovillous adenoma with high-grade dysplasia**.

A follow-up surgery was scheduled for October 2025, but the procedure was postponed due to the patient's concurrent cold. In November 2025, the patient underwent a sentinel lymph node biopsy (SLNB) and extensive local excision of the primary tumor site with a clinical margin of at least 1 cm. Both procedures were performed in accordance with oncological surgical principles applicable to melanocytic tumors of uncertain biological behavior.

The final histopathological examination of the re-excision

specimen revealed no residual tumor; the sentinel lymph node was negative for metastases; and no histological features of malignancy were observed. These findings confirmed the complete removal of the malignant lesion.

The patient's medical history revealed a high tumor burden. The patient's father had stomach cancer (at age 34), father's brother had a brain tumor (in his 70s), cousin had a brain tumor, and paternal grandfather was diagnosed with an unspecified tumour at a young age. In view of the significant family history, the patient was referred for genetic testing.

A heterozygous, likely pathogenic mutation in the BAP1 gene was detected: NM_004656.4(BAP1): c.255+2T>C p.?. This is a splicing-affecting mutation. According to HGMD, the mutation is pathogenic (CS1710694). Pathogenic mutations in the BAP1 gene are associated with BAP1 tumor predisposition syndrome (BAP1-TPDS; MIM: 603089); the individual in question has an increased risk of developing various tumors, including skin melanoma, meningioma, malignant mesothelioma, uveal melanoma, basal

cell carcinoma, renal cell carcinoma, and bile duct carcinoma (GeneReviews; NBK390611). The individual's offspring have a 50% chance of carrying the identified mutation. Analysis of exon deletions/duplications using the DeCON program has ruled out deletions and duplications in the BRCA1, BRCA2, CHEK2, TP53, and CDH1 genes. **BAP1 tumour predisposition syndrome (BAP1-TPDS)** is a rare hereditary cancer syndrome associated with an increased risk of developing a broad spectrum of tumours. Such as, for example, uveal melanoma, skin melanoma, malignant mesothelioma, basal cell carcinoma, renal cell carcinoma, and, less commonly, other tumors.

MDT Consultation: Adjuvant immunotherapy with nivolumab for 1 year is indicated. Prescribed adjuvant treatment: Nivolumab 480 mg intravenously.

Follow-up CT scan: native computed tomography of the brain; contrast-enhanced computed tomography of the brain, facial bones, neck, chest, abdomen, and pelvis in June 2026. There are small areas of consolidation in the lungs, most of which remain stable compared to the October 2025 examination. In the lower lobe of the left lung, there is a small nodule in S9, 3-4 mm in diameter, which was not clearly distinguishable on the previous scan to be re-evaluated in 3 months. Opinion/Recommendations: The nodule in the left lung should be re-evaluated in 3 months. Otherwise, no significant findings [1-11].

Discussion

Malignant Transformation of Cellular Blue Nevus

Cellular blue nevi are generally benign but may extend deeply and incompletely excised lesions can persist. Rarely, stepwise molecular progression may lead to melanoma. Melanoma arising in association with a blue naevus frequently lacks an intraepidermal component, as observed in the present case, and may remain confined to the dermis or subcutaneous tissue, thereby complicating the application of conventional melanoma staging criteria.

The management of cellular blue naevi generally involves complete surgical excision followed by histopathological evaluation. In cases where lesions exhibit substantial depth or where excision margins are uncertain, some authors advocate re-excision or regular clinical surveillance. However, owing to the rarity of malignant transformation, evidence-based management recommendations remain limited, and standardised clinical guidelines have yet to be established. In the case under review, a depth of 8 mm is quite deep for a benign nevus, especially when compared to typical skin lesions, and therefore would have required immediate and more serious attention due to the possibility of malignancy.

Role of BAP1 Inactivation

Primary driver mutations in blue nevi frequently involve **GNAQ** or **GNAI1**. Malignant transformation is thought to require additional genetic alterations. BAP1 is a tumor suppressor gene involved in chromatin regulation and DNA damage response. Loss of BAP1 expression has been implicated in melanocytic tumor progression and is associated with:

- Increased tumor aggressiveness.
- Higher metastatic potential in some series.
- Possible germline predisposition (BAP1 tumor predisposition syndrome).

In this case, BAP1 loss supports molecular progression from residual cellular blue nevus to melanoma.

Clinical Implications

Several aspects of this case are noteworthy:

1. Indeterminate margins in 2016 likely allowed residual tumor persistence.
2. Early postoperative regrowth suggested incomplete excision.
3. Long-term slow enlargement masked malignant transformation.
4. Satellite nodules mimicked multifocal benign recurrence.
5. A thorough family history was not obtained during the initial treatment.

Although imaging demonstrated a well-circumscribed lesion and the radiological findings were considered more suggestive of a benign process, histopathological examination ultimately revealed an invasive melanoma.

Prognosis

pT4 melanoma (>4 mm thickness) carries substantial risk of recurrence and metastasis, even in the absence of nodal involvement. Negative SLNB is prognostically favorable but does not eliminate risk. Lifetime risk of developing mesothelioma, uveal melanoma, and cutaneous melanoma: approximately 20-25%. The risk of renal cell carcinoma and other related tumors is lower. The lifetime risk of developing at least one BAP1-related tumor may be as high as 85%. It should be noted that the actual risk may be lower, as previous estimates may have been influenced by the very narrow selection of subjects studied. The patient's offspring have a 50% probability of inheriting the identified genetic variant and, consequently, of being at increased risk of developing associated tumours.

Long-term oncologic surveillance is mandatory. Active surveillance is recommended and should include regular ophthalmological examinations, annual dermatological assessment comprising a full-body skin examination with dermoscopy, and annual renal imaging, with magnetic resonance imaging (MRI) as the preferred modality. Surveillance for other BAP1-associated malignancies may be undertaken using appropriate cross-sectional imaging, including computed tomography (CT), where clinically indicated.

Cascade genetic testing should first be offered to the patient's siblings and to the offspring of the patient's parents. The patient's own offspring should also be offered predictive genetic testing and appropriate surveillance upon reaching adulthood, or earlier if clinical features suggestive of BAP1 tumour predisposition syndrome become apparent [1-11].



Figure 3: High-power histopathological and immunohistochemical features of BAP1-inactivated melanoma.

Conclusion

This case highlights the potential clinical consequences of uncertain surgical margins in the absence of structured postoperative surveillance following the excision of a deep cellular blue naevus. Although malignant transformation of blue naevi is rare, structured follow-up and clearly defined surgical management strategies may facilitate earlier detection of malignant change. Greater awareness of these management principles may improve the early recognition of malignant transformation and optimise clinical outcomes in patients with deep melanocytic lesions.

References

1. Mishima Y. (1970). Cellular blue nevus: melanogenic activity and malignant transformation. *Arch Dermatol*. 101: 104-110.
2. Zembowicz A, Phadke PA. (2011). Blue nevi and variants. *Arch Pathol Lab*. 135: 327-336.
3. Henning A, Billings S, Ko J, Weaver J. (2021). Atypical cellular blue nevus with necrosis mimicking melanoma ex-blue nevus. *Am J Dermatopathol*. 43: 61-64.
4. Aloï F, Pich A, Pippione M. (1996). Malignant cellular blue nevus: a clinicopathological study. *Dermatology*. 192: 36-40.
5. Loghavi S, Curry JL, Torres-Cabala CA, Ivan D, Patel KP, et al. (2014). Melanoma arising in association with blue nevus: a clinical and pathologic study of 24 cases. *Mod Pathol*. 27: 1468-1478.
6. Popov H, Pavlov P, Stoyanov GS. (2025). Blue nevi and melanoma arising in blue nevus: a comparative histopathological case series. *Reports*. 8: 131.
7. Daltro LR, Yaegashi LB, Freitas RA, Fantini BDC, da Silva CS. (2017). Atypical cellular blue nevus or malignant blue nevus? *An Bras de Dermatol*. 92: 110-112.
8. Yeh I, Fang Y, Busam KJ. (2012). Melanoma arising in a large plaque-type blue nevus with subcutaneous nodules. *Am J Surg Pathol*. 36: 1258-1263.
9. <https://www.ncbi.nlm.nih.gov/books/NBK390611/>
10. Lalloo F, Kulkarni A, Chau C, Nielsen M, Sheaff M, et al. (2023). Clinical practice guidelines for the diagnosis and surveillance of BAP1 tumour predisposition syndrome. *European Journal of Human Genetics*. 31: 1261-1269.
11. Cooper DN, Ball EV, Stenson PD, Phillips AD, Evans K, et al. (2017). The Human Gene Mutation Database (HGMD®) represents an attempt to collate known (published) gene lesions responsible for human inherited disease. and is maintained in Cardiff.