Clinicopathological study of blue nevi of the gastrointestinal (GI) tract: first case series

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ABSTRACT

Aim Blue nevus (BN) is a benign melanocytic proliferation that is typically cutaneous. Extracutaneous BN is infrequent and is reported in the mucosa of various organs. Gastrointestinal (GI) tract BN is rare. Here, we describe the clinicopathological findings of the largest series of GI tract BNs.

Methods A search of our Pathology Data System (1984–2019) identified six GI tract blue nevi. Clinical information, pathology reports and available H&E-stained section slides were reviewed.

Results Lesions predominated in the middle-aged adults (mean 54, range 27–80) with a slight female predominance (66%). Most cases arose in the rectum and colon (83%), with one gastric lesion (17%). Four cases were identified during endoscopic examination performed either for screening or for unrelated symptoms (66%). Two patients presented with rectal bleeding (33%) unassociated with the BN. Endoscopically, most lesions appeared as superficial hyperpigmented areas (83%). One case was described as abnormal mucosa (17%). Microscopically, the mucosa was involved in all of the cases (100%). One case showed submucosal extension in addition to the mucosal component (17%). Lesions showed a proliferation of bland spindle cells with abundant granular pigment. No nuclear atypia or mitoses were identified. Immunostains showed immunoreactivity for melanocytic markers. Follow-up information available for five patients showed no recurrences to date (mean follow-up 1 year).

Conclusions BN is a benign melanocytic proliferation. It is important to be aware of the occurrence of such lesions outside of the skin and consider the possibility of BN when pigmented lesions are encountered in the GI tract.

INTRODUCTION

Blue nevi (BNs) are benign melanocytic skin lesions that are commonly encountered in routine pathology practice. Cutaneous BNs were first described by Tièche in 1906.[1] They are believed to arise from an abnormal arrest in embryonal migration of neural crest melanocytes.[2]

Clinically, BNs of the skin present as small (usually less than 1 cm), raised, blue to purple papules with regular borders. They most commonly arise in the dorsal aspect of the extremities, the scalp, and less commonly on the trunk and the buttocks.[3] Skin BNs are generally classified into common BN and cellular BN. However, other variants (amelanotic, desmoplastic, deep penetrating, atypical and malignant) have been described.

Histologically, common BNs are composed of variably pigmented bland spindled melanocytes in the superficial or papillary dermis with an inverted wedge-shaped configuration. Some degree of stromal desmoplasia is often seen but typically there is no significant nuclear atypia or mitotic activity. Melanophages can also be a prominent cell constituent in common BNs.[3]

Cellular BNs usually occur in younger adults (less than 40 years old). These lesions are typically larger (1–2 cm) blue-black dome shaped lesions of the buttocks, sacral area or the scalp. Histologically, cellular BNs are often biphasic lesions consist of areas of classic BN admixed with distinct cellular areas. The cellular areas are composed of spindle to oval melanocytes with clear to finely pigmented cytoplasm. Cellular BNs may extend deeper to the subcutaneous tissue. Cellular BNs were once thought to be related to malignant melanoma; however, they are now recognised as a benign neoplasm related to BNs.[3]

Immunohistochemically, the cells of BNs stain positively for melanocytic markers such as S100 protein, MART-1 and HMB-45.

Although rare, extracutaneous BNs have been reported in mucosal surfaces that are normally devoid of melanocytes, such as the oral and sinonasal mucosa, oesophagus and the female genital tract (vagina and uterine cervix). Some other

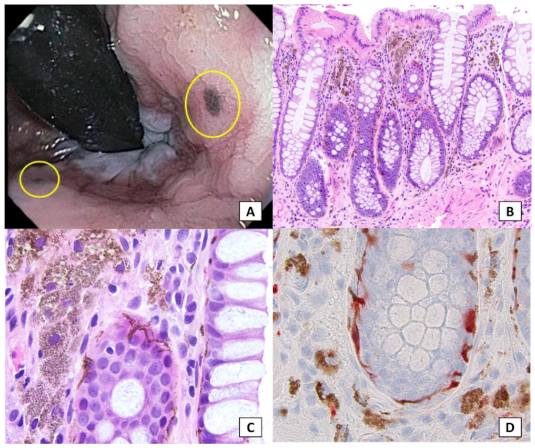

Figure 1 (A) Endoscopic appearance of pigmented lesion arising in the rectum. (B) Colonic mucosa with the proliferation of bland pigmented cells in the lamina propria. (C) Higher magnification showing the admixture of pigmented dendritic cells and melanocytes in the lamina propria. (D) S100 immunohistochemistry highlights the melanocytes.

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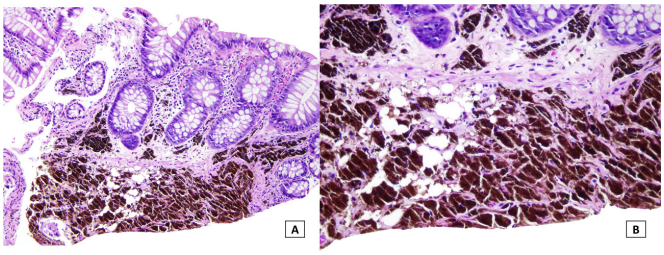

Figure 2 (A) Colonic mucosa with the proliferation of bland pigmented cells in the mucosa with extension to the submucosa. (B) Higher magnification showing the pigmented cells in the submucosa.

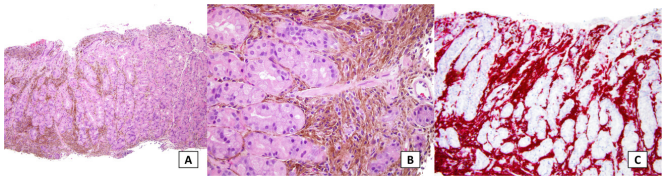

Figure 3 (A) Gastric oxyntic mucosa with pigmented cells in the lamina propria (low power). (B) Spindle and dendritic melanocytes, heavily pigmented, without cytologic atypia (higher magnification). (C) Immunohistochemical stain for Mart1 highlights the melanocytes.

reported locations are spermatic cord, prostate and lymph nodes.[4–12]

BNs of the gastrointestinal (GI) tract are exceedingly rare. Our literature review revealed a few case reports of rectal BNs.[13–15] GI tract BNs display features similar to those of their cutaneous counterparts and consist of a proliferation of bland, heavily pigmented spindled mucosal melanocytes. Rarely, the pigmented melanocytes extend into the submucosa. The cells have abundant granular cytoplasm filled with melanin pigment and show no cytologic atypia or mitotic figures.[3 4]

Although BNs are commonly recognised as spindle cell lesions, occasionally the melanocytes can appear epithelioid. In such cases, they are best classified as epithelioid BNs. Epithelioid BNs are important to recognise as they can have syndromic associations with the Carney complex.[16] Individuals with Carney complex disorder have an increased risk of developing several types of tumours. Affected individuals usually have skin pigmentations, cardiac myxomas or myxomas of other parts of the body, and tumours of endocrine organs such as adrenal, thyroid and the pituitary glands. Other associated lesions are epithelioid BNs and psammomatous melanotic schwannoma, which has more recently been termed malignant melanotic schwannian tumour.[16] Mutations in the *PRKAR1A* gene encoding the R1a regulatory subunit of protein kinase A that is found on chromosome 17q22-24 have been reported in patients with the Carney complex.[3,17]

MATERIALS AND METHODS

A search of the Pathology Data System (PDS) of the Johns Hopkins Hospital from 1984 to 2019 identified six BNs of the GI tract. Clinical information, gross description, pathology reports and available H&E-stained section slides (available in two cases) were reviewed. All cases had been reviewed in consultation by one of the authors (EAM) and demographic information was available for all of the cases. The following histopathological findings were recorded: the location of the lesion, the layer/s of the GI tract involved, characteristics of the spindle cells, presence of nuclear atypia, mitoses or necrosis. Available immunohistochemical stains were also reviewed.

RESULTS

Lesions predominantly were seen in middle-aged adults with a mean age of 54 years (range 27–80) and a slight female predominance (n=4, 66%). The most common sites were rectum and colon (n=5, 83%), followed by the stomach (n=1, 17%). Four cases were identified incidentally during the endoscopic examination that was performed either for screening or for unrelated symptoms (n=4, 66%). Two patients presented with rectal bleeding (n=2, 33%) related to haemorrhoids, but unassociated with the BN. Endoscopically, most lesions appeared as superficial hyperpigmented areas (n=5, 83%) (figure 1). One case was described as abnormal mucosa (n=1, 17%). Microscopically, the mucosa was involved in all the cases (n=6, 100%). One case showed superficial submucosal extension in addition to the mucosal component (n=1, 17%) (figure 2).

Microscopically, the lesions were composed of a proliferation of bland spindle cells with abundant granular pigment (figure 1). The spindle cells displayed bland, ovoid, vesicular nuclei, inconspicuous nucleoli and granular pigmented cytoplasm. No nuclear atypia, mitoses or necrosis were identified. When performed, immunostains showed strong immunoreactivity for melanocytic markers (S100 protein, HMB45 and MART1) (figures 1 and 3). Histologically, all cases showed features of common BNs with the admixture of pigmented dendritic cells and melanocytes. No features to suggest any other described variants of BNs were identified. Follow-up information was available for five patients with no recurrences reported to date (mean follow-up 1 year). None of our cases showed the histological features of an epithelioid BN or the clinical history that prompt us to consider the Carney complex. No history of melanoma was noted in any of our cases. The clinicopathological data are summarised in table 1.

Table 1 Clinicopathologic summary of six GI tract blue nevi

Case no.	Demographics (age/sex)	Clinical presentation	Endoscopic appearance	Location	Layer of GI tract
1	80/F	Nausea	Discoloured gastric mucosa	Stomach	Mucosa
2	39/F	Rectal bleeding	Superficial hyperpigmented area	Rectum	Mucosa
3	27/M	Rectal bleeding	Hyperpigmented area	Rectum	Mucosa
4	64/F	Screening colonoscopy	Hyperpigmented area	Anorectal junction	Mucosa
5	72/M	Screening colonoscopy	Hyperpigmented lesions	Transverse colon	Mucosa
6	42/F	Screening colonoscopy	Abnormal mucosa	Rectum	Mucosa

GI, gastrointestinal.

Box 1 Differential diagnosis for pigmented gastrointestinal tract lesions

Metastatic or mucosal malignant melanoma
Psammomatous melanotic schwannoma/malignant melanotic schwannian tumour
Pigmented neuroendocrine tumours
Epithelioid leiomyoma

DISCUSSION

BN is a rare benign lesion that can arise in the GI tract. Given its rarity in the GI tract, correct identification is important in order to distinguish this benign lesion from other mesenchymal GI tract lesions. Based on our findings, BNs of the GI tract are mainly seen in the colon and rectum, followed by the stomach. GI tract BNs are usually asymptomatic and incidentally found during endoscopic examination.

GI BNs are histologically similar to their cutaneous counterparts in that they are moderately cellular pigmented lesions composed of bland cells with spindled vesicular nuclei, inconspicuous nucleoli and granular pigmented cytoplasm. Necrosis is universally absent and mitoses are exceedingly rare.

It has been postulated that rectal BNs can either originate from anal melanocytes or rectal mucosa.[2] One of our cases arose in the anorectal region but it is unclear if this was as a result of the migration of anal melanocytes or whether it originated from the rectum. GI tract BNs should be differentiated from other pigmented spindle cell mesenchymal lesions such as psammomatous melanotic schwannoma and metastatic malignant melanoma (box 1).

Psammomatous melanotic schwannoma is also termed malignant melanotic schwannian tumour since a subset of these lesions has been shown to behave unpredictably and occasionally metastasise.[18] It is a rare pigmented lesion that can be seen in the setting of Carney's complex and should be considered in the differential diagnosis of pigmented lesions of the GI tract. Clinically, those of the GI tract are typically an incidental finding in contrast to those that arise in the paraspinal tissues.[19] Histologically, GI tract examples show plump-pigmented epithelioid and spindled cells with psammomatous calcifications. Psammomatous calcifications can be only present focally. Lesional cells can have degenerative type atypia with markedly enlarged hyperchromatic 'smudgy' nuclei. Mitoses can also be seen.[20]

The pigmented nature of BNs may raise concerns for metastatic melanoma or malignant mucosal melanoma, especially in the anorectal region. Clinically, anorectal malignant melanomas present as polypoid masses associated with pain, rectal bleeding and obstruction, whereas BNs are often asymptomatic and are usually an incidental finding during endoscopy.[21] By histological examination, malignant melanomas show nuclear pleomorphism and atypia with mitoses, features that are absent in BNs (table 2). In mucosal melanoma, the presence of atypical junctional melanocytes and atypical melanocytic cells in the basal layer of the superficial epithelium could also be helpful in making the diagnosis.

At a molecular level, mutations that are implicated in the pathogenesis of common nevi or malignant melanoma such as *BRAF*, *NRAS* or *KIT* are not reported in BNs and their variants.[3 22] Additionally, somatic mutations in *GNAQ* have been documented by various studies in skin BNs.[23 24]

Table 2 Histological features of GI tract blue nevi in comparison to mucosal malignant melanoma

Blue nevi	Mucosal malignant melanoma
Uniform cells	Pleomorphism
Bland nuclei	Nuclear atypia
Inconspicuous nucleoli	Prominent nucleoli
Rare mitotic figures	Frequent mitoses

Classic BNs are easy to recognise and diagnose; however, their rarity in the GI tract may cause diagnostic dilemmas or confusion with other GI mesenchymal lesions and melanoma.

Other neoplasms to consider when a pigmented lesion is encountered in the GI tract are pigmented neuroendocrine tumours or epithelioid leiomyomas. These lesions, if suspected, can be easily distinguished from others by the use of immunohistochemistry.

In conclusion, we have reported the largest case series to date of GI tract BNs. This uncommon lesion has a predilection for adults and a slight female predominance. The clinical course is benign and neither our study nor our review of the literature identified any malignant examples. Unlike mucosal malignant melanomas of anorectal region, which are symptomatic and present with polypoid masses, rectal bleeding and/or pain, BNs are often an incidental finding. Overall, these lesions seem to be similar to their somatic skin counterparts with no major histological differences. GI tract BNs should be distinguished from other mesenchymal GI tract lesions in order to avoid unnecessary interventions. Although these lesions are rare, further molecular studies to assess for *GNAQ* mutations, which have been known to occur in skin BNs, may be worthwhile.

Take home messages

- Blue nevi (BNs) are benign tumours that rarely occur in the gastrointestinal (GI) tract.
- They predominantly occur in middle-aged adults with a slight female predominance.
- The most commonly involved sites are the mucosa of the rectum, colon and the stomach.
- They are hypocellular pigmented spindle cell lesions.
- It is important to be aware of the occurrence of BNs in extracutaneous sites, including the GI tract.

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Contributors NA gathered the data, reviewed the slides and wrote the manuscript. KS, DH and ALW performed data acquisitions and reviewed the manuscript. LV supervised the process and reviewed the manuscript. EAM, the senior author, supervised the study, provided the cases for the study from her consultation service, reviewed the slides and reviewed the manuscript.

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