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Cutaneous Manifestations in Neuroblastoma: Clinicopathological Spectrum, Diagnostic Challenges, and Prognostic Implications

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ABSTRACT

Background: Neuroblastoma is the most common extracranial solid malignancy in children, accounting for approximately 8–10% of pediatric cancers and 15% of cancer-related mortality. Cutaneous metastases, although relatively uncommon, represent an important clinical manifestation often associated with disseminated disease.

Aim: To comprehensively analyze the clinical spectrum, pathogenesis, diagnostic approach, and prognostic implications of cutaneous manifestations in neuroblastoma.

Methods: A narrative review of published literature (2000–2025) integrated with clinicopathological insights was conducted focusing on dermatological manifestations of neuroblastoma.

Results: Cutaneous lesions most commonly present as bluish nodules ("blueberry muffin lesions"), resulting from dermal infiltration by malignant neuroblasts. These are frequently associated with Stage IV or Stage MS disease. Diagnosis relies on histopathology, immunohistochemistry, and imaging modalities such as MIBG scan. Molecular markers such as MYCN amplification significantly influence prognosis.

Conclusion: Cutaneous manifestations serve as critical diagnostic and prognostic indicators in neuroblastoma. Early recognition and appropriate evaluation can significantly impact staging, therapeutic decisions, and survival outcomes.

KEYWORDS: Neuroblastoma, Cutaneous Manifestations, Skin Metastasis, Clinicopathological Spectrum, Histopathology, Immunohistochemistry, Diagnostic Challenges, Differential Diagnosis, Skin Biopsy, Disease Outcome, Tumor Staging, Risk Stratification, Pediatric Skin Lesions, MYCN Amplification

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INTRODUCTION

Neuroblastoma is a malignant tumor arising from primitive neural crest cells that form the sympathetic nervous system, most commonly originating in the adrenal medulla or paraspinal sympathetic chain [1,2]. It predominantly affects children under 5 years of age, with peak incidence in infancy.

The disease is characterized by marked biological heterogeneity, ranging from spontaneous regression to aggressive metastatic progression. Approximately 50–60% of patients present with metastatic disease at diagnosis, commonly involving bone marrow, liver, lymph nodes, and skin [3].

Cutaneous metastases are particularly characteristic in infants and may manifest as the classic "blueberry muffin" appearance, representing dermal infiltration by tumor cells [4]. This clinical presentation overlaps with other neonatal conditions such as congenital TORCH infections and hematologic disorders, posing significant diagnostic challenges.

Recent advances in tumor biology have highlighted the role of genetic and molecular alterations such as MYCN amplification, ALK mutations, and Trk receptor expression in determining tumor behavior and prognosis [5,6]. These biomarkers have become integral to risk stratification and therapeutic planning.

Despite advances in imaging and molecular diagnostics, cutaneous manifestations remain an important early clinical clue in certain cases. Their recognition is crucial not only for diagnosis but also for staging and prognostic assessment.

PATHOGENESIS AND MOLECULAR BASIS

Cutaneous involvement in neuroblastoma occurs primarily through hematogenous dissemination of tumor cells, which subsequently localize within dermal capillaries and proliferate.

Key mechanisms include:

- **Hematogenous Spread:** Circulating neuroblasts seed the dermis via vascular channels [7]
- **Tumor Microenvironment Interaction:** Tumor cells interact with dermal fibroblasts and extracellular matrix, facilitating growth and survival
- **Angiogenesis:** Overexpression of VEGF promotes vascular proliferation and tumor expansion [8]
- **Genetic Alterations:**
  - **MYCN amplification:** Strongly associated with aggressive disease and poor prognosis
  - **ALK mutations:** Implicated in familial and sporadic neuroblastoma
  - **Trk receptor expression:** Correlates with tumor differentiation and outcomes

CLINICAL SPECTRUM

Cutaneous manifestations vary in morphology and clinical significance:

Common Presentations

- Bluish or violaceous nodules
- Firm, non-tender subcutaneous lesions
- Blanching lesions on pressure
- Rapid progression in aggressive disease

Special Presentations

- Blueberry muffin lesions: Classic neonatal presentation
- Diffuse cutaneous infiltration: Rare, severe form
- Paraneoplastic syndromes: Opsoclonus-myoclonus syndrome (rare association)

DIAGNOSTIC APPROACH

Accurate diagnosis requires a multidisciplinary approach:

Clinical Evaluation

- Multiple bluish nodules in infants
- Associated hepatomegaly or systemic features

Laboratory Investigations

- Elevated urinary catecholamines (VMA, HVA) [9]
- Serum neuron-specific enolase (NSE)

Imaging

- Ultrasound abdomen (primary tumor screening)
- CT/MRI for staging
- **MIBG scintigraphy** (gold standard for detecting metastasis) [10]

Histopathology & Immunohistochemistry

- Small round blue cell tumor morphology
- Homer-Wright rosettes
- Immunopositivity for:
  - NSE
  - Synaptophysin
  - Chromogranin

DISCUSSION

Cutaneous manifestations in neuroblastoma represent a unique clinical entity with both diagnostic and prognostic implications. Although generally indicative of systemic dissemination, their presence in infants—particularly in Stage MS disease—may paradoxically be associated with favorable outcomes [11].

The classic “blueberry muffin” appearance is a key dermatological sign that should prompt immediate evaluation for underlying malignancy. However, this presentation overlaps with congenital infections such as TORCH, often leading to diagnostic delays. Therefore, early biopsy and biochemical evaluation are critical for accurate diagnosis.

The present review supports existing literature demonstrating that cutaneous metastases occur in approximately 5–10% of neuroblastoma cases and are more frequently observed in infants [12]. These lesions often coexist with liver and bone marrow involvement, reflecting widespread disease.

From a molecular standpoint, MYCN amplification remains one of the most important prognostic markers, strongly associated with aggressive disease and poor survival irrespective of clinical presentation [5]. Conversely, tumors without MYCN amplification and those expressing TrkA receptors tend to exhibit favorable biology and may even undergo spontaneous regression.

Therapeutically, management strategies are guided by risk stratification:

- **Low-risk disease:** Observation or minimal intervention
- **Intermediate-risk:** Chemotherapy ± surgery
- **High-risk:** Intensive multimodal therapy including chemotherapy, surgery, radiotherapy, and immunotherapy

Interestingly, cutaneous lesions often regress in response to systemic therapy, serving as a visible marker of treatment response. In Stage MS disease, spontaneous regression of both primary and metastatic lesions—including skin lesions—has been well documented [13].

Despite these insights, challenges remain in early diagnosis, especially in resource-limited settings. Increased awareness among dermatologists and pediatricians is essential for prompt recognition and referral.

PROGNOSTIC SIGNIFICANCE

Favorable Factors

- Age <1 year
- Stage MS disease
- Absence of MYCN amplification

Poor Prognostic Factors

- Stage IV disease
- MYCN amplification
- Rapid disease progression

CONCLUSION

Cutaneous manifestations in neuroblastoma are clinically significant indicators that aid in early diagnosis, staging, and prognostication. While often associated with metastatic disease, their presence in infants may indicate a unique biological subset with favorable outcomes. Early recognition, histopathological confirmation, and integration of molecular markers are essential for optimal management and improved survival.

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