Journal of Pigmentary Disorders
ISSN: 2376-0427

Iyengar, Pigmentary Disorders 2015, 2:6
DOI: 10.4172/2376-0427.1000188

Research Article Open Access

Halo Nevus – the Vascular Connection

Bhanu Iyengar*

Pigment Cell Center, New Delhi, India

Abstract

Background: Halo Nevi (HN), are defined as benign melanocytic nevi that are surrounded by a rim of depigmentation, resembling a halo. The halo phenomenon indicates the involution and subsequent regression of the melanocytic nevus.

Material and Methods: A random series of 137 nevi, including 75 HN were examined. Serial paraffin and frozen sections were subjected to: routine histochemistry; (HE, Reticulin, Auro, PAS), enzyme histochemistry: dopa oxidase, counterstained with Nuclear Fast Red (NFR) to highlight the endothelium and dopamine oxidase; immunohistochemistry to assess presence of lymphocytic infiltrates; electron microscopy: after enbloc dopa stain.

Results and Discussion: Junctional nevi show proliferation of highly dendritic melanocytes within the epidermis. Intradermal nevi are composed of dermal nevus cells separated from the epidermis by a clear Grenz zone. Compound nevi show a combination of junctional activity and sheets of dermal nevus cells. Some nevi show a depigmented halo and can regress completely to be replaced by a depigmented patch, the halo nevus. The nevus cells and marginal melanocytes are replaced by endothelial cells, lining vascular spaces, with involution of the nevus.

Intriguingly there is a complete absence of inflammatory and immune related lympho-histiocytic cells in the cases studied. These observations, suggest that nevus cells are replaced by vascular endothelial cell types which results in dissolution of the lesion.

Keywords: Halo nevus; Trans-differentiation; Melanocytes; Endothelial cell

Introduction

Halo Nevi (HN), also termed Sutton nevi [1], leukoderma acquisitum centrifugum, or halo phenomenon, are defined as benign melanocytic nevi that are surrounded by a rim of depigmentation, resembling a halo [2-8]. The halo phenomenon often indicates the beginning of involution and subsequent regression of the melanocytic nevus, a process that extends over a period of several months [9].

The halo phenomenon is most common in benign melanocytic nevi but it may also be observed in other benign or malignant neoplasms such as blue nevi, Spitz juvenile nevi [10], neurofibromas, seborrhoeic keratoses, dermatofibromas, basal cell carcinomas and malignant melanomas [6,8]. HN is often associated with vitiligo [11,12] and rarely with melanoma [13-16] and choroidal nevi [17,18].

The causes of both vitiligo and halo nevi are poorly understood. An immune-mediated process has been suggested. Four sequential stages of mononuclear infiltrate of macrophages, cytotoxic T cells, and Langerhans cells have been described [13,19,20].

Patients with halo nevi have circulating antibodies to cytoplasmic antigens in melanoma cells [19,21]. Halo reaction can also cause increased cytologic atypia in lesional melanocytes and obscure the architectural features of the underlying nevus, making distinction between a benign melanocytic nevus and melanoma difficult [10]. The mode of involution of nevi has been studied in depth since the present series of cases shows a complete absence of infiltrates.

Material and Methods

The present study includes a random series of 137 Nevi, 75 being Halo Nevi associated vitiligo, received from the Dermatology Unit of Safdarjung Hospital, New Delhi, fixed in 10% formol glutaraldehyde.

The nevi were received as excision biopsies to include the entire lesion. Serial 5 µm thick, frozen and paraffin [20-33] sections from each block, were maintained at 4°C. These were subjected to: routine histochemistry; (HE, Reticulin, PAS), enzyme histochemistry: Dopa Oxidase counterstained with nuclear fast red to highlight endotheliaal cells; immunohistochemistry; electron microscopy: routine and after enbloc stain for dopa [22-24].

Results

Pigmented nevi: (Figure 1)

Junctional Nevi (JN): Flat pigmented nevus showing junctional activity with proliferation of prominent highly dendritic epidermal melanocytes within the epidermis. The underlying dermis does not show any pigment cells (Figure 1a).

Intradermal Nevi: (IDN) These pigmented lesions are slightly raised and show increased epidermal pigmentation and prominent epidermal dendritic melanocytes [25,26]. Sheets of closely packed nevus cells are seen in the underlying dermis separated from the epidermis by a clear Grenz zone. The nevus cells of the layers adjacent to the epidermis are pigmented being induced by the epidermal dendritic melanocytes, while the inner layers are poorly pigmented but show dopa positivity. The nevus cells show features of Schwannian cells. The cells are arranged in sheets with no definite vascular channels (Figure 1b).

Compound Nevi: (CpN) Show a combination of the above with junctional activity showing proliferation of epidermal dendritic melanocytes which grow down to intermingle with underlying sheets of Schwannian nevus cells with pigmentation throughout the lesion. The cells are arranged in sheets with no definite vascular channels. Occasional groups of cells are seen to surround clear spaces in the depth of the lesion (Figure 1c).

***Corresponding author:** Bhanu Iyengar, Iyengar Farm, Brijwasan Road, PO Kapashera, New Delhi110037 India, Tel: 022-2898 3610; E-mail: bhanu_i@yahoo.com

Received April 14, 2015; **Accepted** May 15, 2015; **Published** May 25, 2015

Citation: Iyengar B (2015) Halo Nevus – the Vascular Connection. Pigmentary Disorders 2: 188. doi:10.4172/2376-0427.1000188

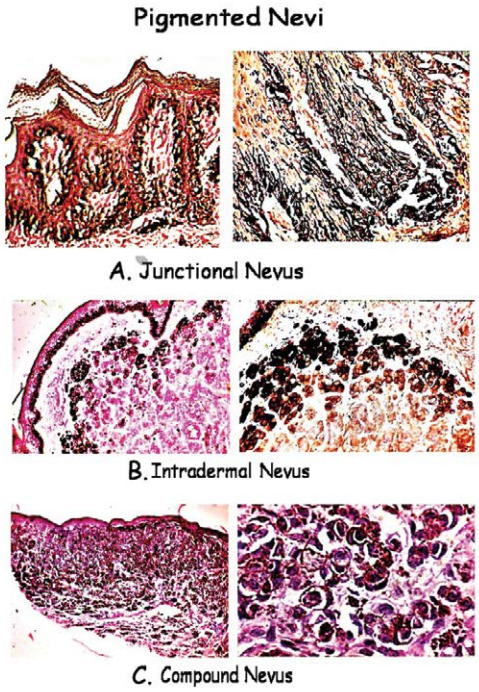

Figure 1: A. Junctional nevus: Prominent dendritic epidermal melanocytes within the basement membrane. **B.** Intradermal nevus: Sheets of nevus cells are seen within the dermis, separated from the epidermis by a clear Grenz zone. **C.** Compound nevus: Both epidermal and dermal components are present. There is heavy pigmentation throughout the lesion.

Halo nevi

All 75 halo nevi were assessed for the process of loss of pigmentation. The lesions show a range of dissolution from initial stages to almost complete depletion of the component cells in the nevus. The periphery shows loss of epidermal melanocytes forming the halo. Occasional pigmented nevi regress completely and are replaced by a vitiliginous patch. One case shows a halo around a capillary hemangioma. (Figures 2-4).

Individual cases

The cases show varying extents of involution and are graded into three groups, 1. Early stage; 2. Moderate dissolution; 3. Complete dissolution. Three random cases in each group are described below.

Early stage: (Figure 2)

Sk1: Section of HN showing thinning of epidermis. To the left, part of the halo is seen with a loss of the epidermal melanocytes. The underlying nevus cells show a graded replacement by flat NFR positive cells. This process is seen throughout the upper layers of the nevus. The NFR cells form channels which are continuous with the dermal vasculature. At the right the vessels blend with the dermis. The left corner shows depletion of nevus cells beneath the epidermis (Figure 2A).

Sk123: A large HN showing a peripheral halo with loss of epidermal melanocytes. The larger part of the IDN shows dopa positive cells lining sinusoidal spaces to be replaced in the depth by NFR positive cells and continue as vascular spaces. An interesting feature is the presence of dopa positive cells lining vascular spaces and joining the dermal vessels. An interesting feature is seen at the extreme left of the section where a number of endothelium lined capillaries are seen. The lining cells are dopa positive with NFR positive nuclei, these vessels extend into the mid dermis (Figure 2B).

Sk205: A large HN showing complete loss of dopa positive cells at the extreme right of the section. Large sinusoidal spaces extend into the dermis. The positive cells are seen along the adjacent rete ridge. The next field shows almost complete replacement of nevus cells. The extreme left shows replacement of nevus by vascular channels, a process which commences in the depth and extends to involve areas beneath the epidermis. Multiple channels are seen merging with dermal vessels (Figure 2C).

Moderate dissolution: (Figure 3)

Sk92: Nevus replaced by vascular channels resembling vasculogenic sinusoids seen in amelanotic melanomas. The surface areas show cells with partial dopa positivity lining the channels (Figure 3A).

Sk141: A large nevus with a prominent junctional component with highly dendritic melanocytes. The underlying dermis shows prominent well formed vascular channels showing partially dopa positive cells underlying the epidermis. Vascular channels are seen contacting the epidermal melanocytes and replacing them (Figure 3B).

Sk170: IDN showing peripheral involution. The underlying nevus shows extensive replacement by sinusoids lined by NFR positive lining cells. Sinusoids are seen to extend into vascular channels and further into dermal vasculature (Figure 3C).

Complete dissolution: (Figure 4)

Sk36: A section showing almost complete dissolution with a small area of pigment positivity in the center. The epidermis shows highly dendritic melanocytes with prominent enzyme positivity. Beneath the Grenz zone nevus cells positive for dopa are replaced by vascular channels lined by NFR cells. These merge with the underlying vasculature (Figure 4A).

Sk45: The nevus is almost completely replaced by vascular spaces connecting with the dermal vessels. A few surface dopa positive cells can be seen under the epidermis (Figure 4B).

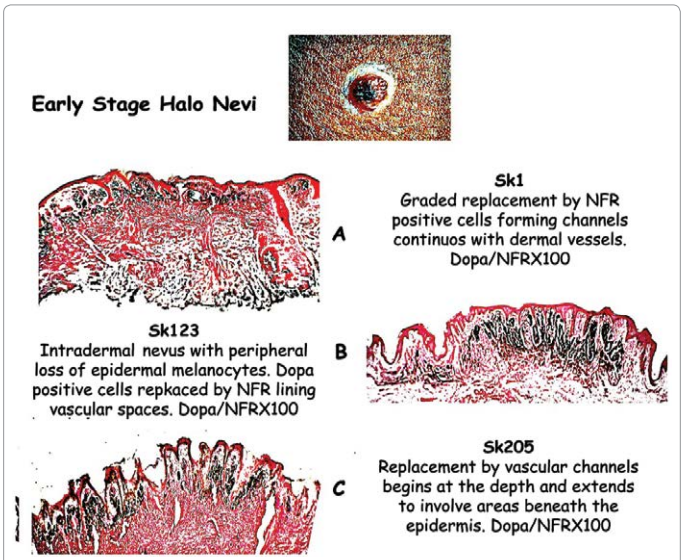

Figure 2: Early stage halo nevus with a ring of depigmentation: Three cases showing initial replacement of dopa positive nevus cells by NFR positive flattened cells at the periphery of the lesion. C shows extensive loss of nevus cells towards the right. [Dopa/NFRX100].

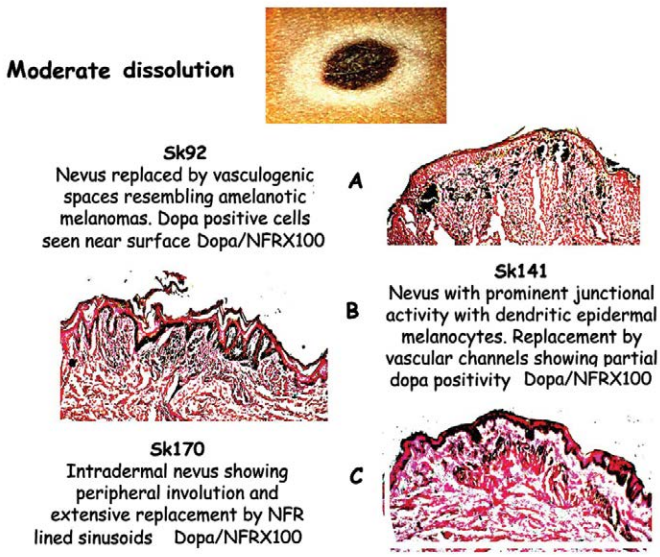

Figure 3: Moderate dissolution of nevus: Three nevi showing large areas of dissolution. **A:** shows replacement of nevus by sinusoidal channels resembling vasculogenesis. **B:** Nevus cells replaced by sinusoidal vascular spaces connecting with dermal vessels. **C:** Very few dopa positive cells remain, mostly replaced by sinusoids. [Dopa/NFRX100].

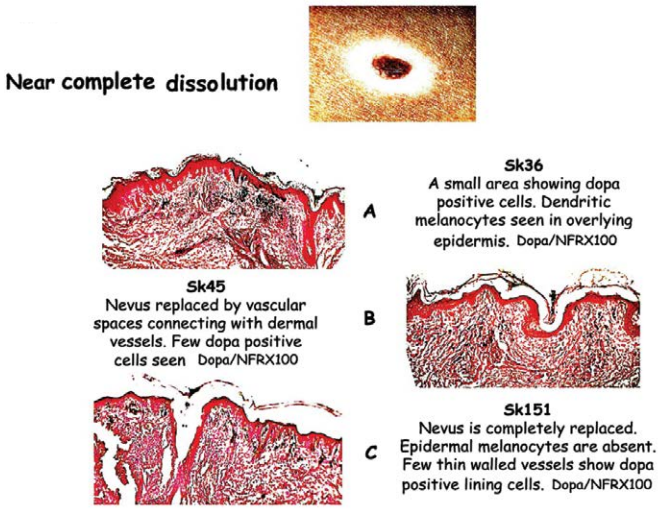

Figure 4: Near complete dissolution of nevus with a large halo and a small zone of pigmentation. Three nevi almost completely replaced by vascular spaces which merge with the dermal vessels. B and C show occasional thin walled vessels with dopa positivity of the lining cells.

Sk151: Nevus is completely replaced. The epidermis show complete absence of melanocytes. The upper dermis shows thin walled vessels with irregular dopa positivity (Figure 4C).

Progress of involution

All 75 halo nevi were assessed for the process of loss of pigment cells. The lesions show a range of dissolution from initial stages to almost complete depletion of the component cells in the nevus. The periphery shows loss of epidermal melanocytes forming the halo. Occasional pigmented nevi regress completely and are replaced by a depigmented vitiliginous patch. The nevus cells do not show necrosis, the NFR positive cells showing viable nuclei. This is corroborated by the absence of reactive infiltrates. Contrary to expectation, on careful scrutiny on HE as well as immunohistochemistry there are no inflammatory infiltrates in any of the samples studied (Figure 5).

Most of the HN are IDN or CpN with initial abundance of nevus cells within the dermis, separated by a Grenz zone in IDN or reaching up to the epidermis and mingling with epidermal melanocytes. Initial changes are in the form of spaces formed within the peripheral and in-depth groups of nevus cells. (Figure 6Ia). On dopa-NFR staining a gradual loss of pigment and dopa is seen with increase in NFR in the lining cells. The process continues to replace cells lining the spaces with NFR positive endothelial cells. As the process extends the nevus cells

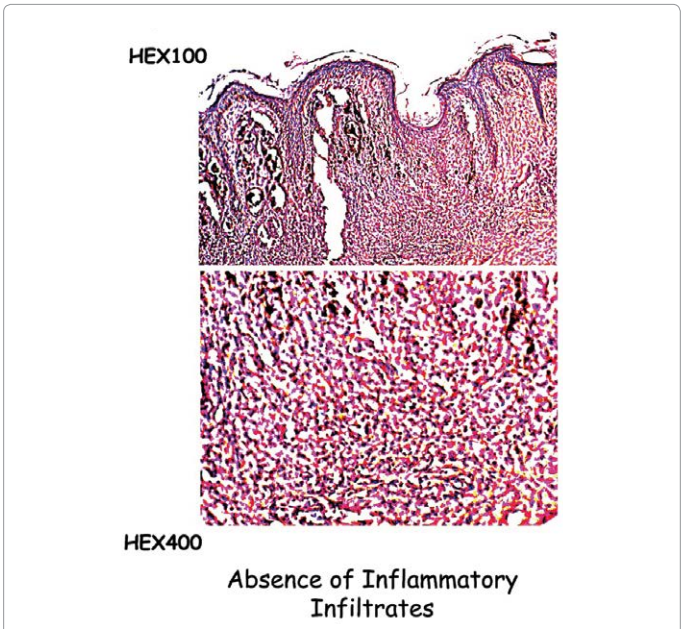

Figure 5: HE stained section of a nevus replaced by vascular channels lined by viable cells. The entire nevus shows a complete absence of inflammatory infiltrates confirmed by the high power view.

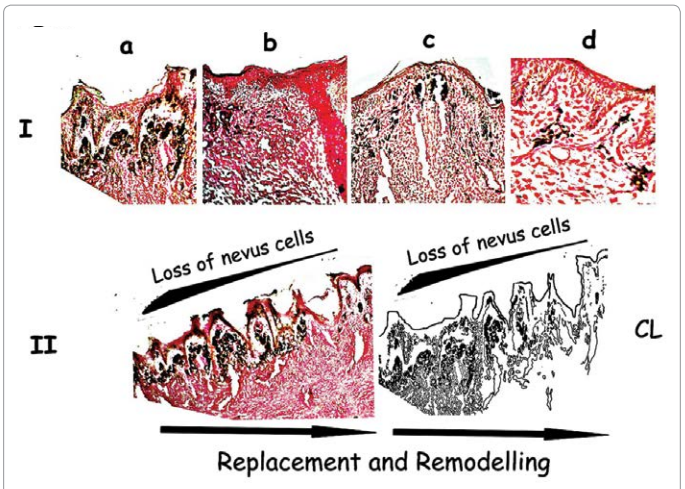

Figure 6: A composite picture showing the different stages of involution. **I: a)** Replacement of dopa positive nevus cells by flattened NFR cells. **b)** NFR cells forming thin walled vessels which connect and merge with dermal vessels. **c)** Replacement by spaces resembling vasculogenesis. **d)** Thin walled vessels showing dopa positivity. **II.** HN showing stepwise replacement of nevus cells by NFR lined vascular spaces. At the right the channels are seen to merge with the dermal vessels with remodeling and fibrous replacement.

are gradually replaced by conjeries of endothelial lined spaces which connect with underlying vasculature. The vessels finally merge and are remodeled to blend with the dermal vessels (Figure 6Ib). In some compact nevus cells are replaced by spaces resembling vasculogenic sinusoids (Figure 6Ic). (Figure 6Id) shows complete dissolution with remnants of dopa positive cells lining thin walled vessels.

Initially spaces lined by flatten dopa positive nevus cells appear at the periphery and depth of the lesion. These do not show PAS or reticulin positive basement membranes. On dopa-NFR staining, a graded loss of dopa is associated with increase in NFR in the flattened lining cells. The nevus cells are replaced by spaces lined with NFR positive flattened cells which are continuous with the endothelial lining of the underlying vasculature to finally merge, and blend with the dermal vessels. The section in (Figure 6II) shows the stepwise involution and replacement by vascular channels. On the right complete involution is seen, the vessels merging with the dermis and reformation of fibrous tissue. The left shows early stages of vascular change. The camera lucida tracings highlight the process (Figure 6IICL).

A similar process is evident in marginal melanocytes. The epidermal melanocytes surrounding the nevus are gradually lost to form a halo. The nevus cells and the epidermal melanocytes are replaced by endothelial cells to result in the involution of the nevus. The process simulates vasculogenesis seen in amelanotic melanomas. Angiogenesis is not elicited from the stromal pre-existing vasculature as observed in melanomas. Thus the nevus cells and the epidermal melanocytes are replaced/converted into endothelial cells to result in the involution of the nevus. The appearance of a halo around a capillary hemangioma is of interest as it links the replacement of nevus cells by endothelial cells with resulting involution.

Discussion

HN usually appears on the back and is common in children and young adults, with a mean age of onset at 15 years [6,27,28]. The incidence of HN in the population is estimated to be approximately 1% and there is no predilection for sex or race [3,29]. Multiple lesions are found in about 50% of the cases.

Four clinical stages have been described beginning with a surrounding rim of depigmentation around a pigmented nevus (stage I), the central nevus loses its pigmentation (stage II) and disappears leaving a circle of depigmentation (stage III). In stage IV the depigmented area undergoes repigmentation, over a period of months or even years [6,9,30]. Most lesions are compound, junctional, or intradermal nevi [8]. Halo nevi, are often associated with concurrent vitiligo [8].

The causes of both vitiligo and halo nevi are poorly understood. An immune-mediated process has been suggested resulting from damage or destruction of melanocytes. Four sequential stages of mononuclear infiltrate of macrophages, cytotoxic T cells, and Langerhans cells have been described [7,13,19,20,30,31].

Patients with halo nevi may have circulating antibodies to cytoplasmic antigens in melanoma cells which disappear upon excision or spontaneous resolution of the central lesion [19,21,32]. Halo reaction can also cause increased cytologic atypia in lesional melanocytes and obscure the architectural features of the underlying nevus, making distinction between a benign melanocytic nevus and melanoma difficult [10].

In the present study, it is observed that occasional pigmented nevi regress completely and are replaced by a depigmented vitiliginous patch. Contrary to expectation, the present series of 75 HN (51 + 24 cases) shows no evidence of inflammatory infiltrates in any of the samples studied at any stage. There are nevi showing a range from initial stages to almost complete depletion of pigment cells in the nevus. The associated epidermis shows loss of peripheral epidermal melanocytes forming the halo.

Most of the HN are Intradermal (IDN) or Compound Nevi (CpN) with initial abundance of nevus cells within the dermis, separated by a Grenz zone in IDN or reaching up to the epidermis and mingling with epidermal melanocytes in CpN. Initial changes are in the form of spaces formed within the peripheral and in-depth nevus cells. The nevus cells flatten to line the spaces. On dopa-NFR staining a gradual loss of pigment and dopa is seen with increase in NFR in the lining cells first in the nuclei followed by the cytoplasm. The process is very similar to vasculogenesis seen in amelanotic melanomas.

The process continues to replace cells lining the spaces with NFR positive endothelial cells. There is no definite evidence of nevus cell necrosis. As the process extends the nevus cells are gradually replaced by conjeries of endothelial lined spaces which connect with underlying vasculature. The vessels finally merge and blend with the stromal vessels. There is no evidence of angiogenesis from the pre-existing stromal vessels or development of Tumor Vascular Complexes (TVCs) as observed in melanomas as seen during tumor angiogenesis [33].

In HN the replacement of melanocytes by endothelium results in involution of the lesion and remodeling of the vascular channels which merge with the pre-existing connective tissue stroma. It is difficult to explain the extremely rare cases of concurrent regression of melanoma on this basis. Two factors are likely to be involved: firstly, a rapid replacement of tumor cells by extensive vascularisation. Secondly, patients with halo nevi may have circulating antibodies to cytoplasmic antigens in melanoma cells which disappear upon excision or spontaneous resolution of the central lesion [19,21,32].

References

1. Sutton RL (1916) An unusual variety of vitiligo (leucoderma acquisitum centrifugum). J Cutan Dis 34: 797-800.
2. Shoham Y, Berezovsky A, Rosenberg L, Krieger Y, Silberstien E, et al. (2009) Halo Nevi – A Decade of Surgical Experience in Southern Israel. The Internet Journal of Plastic Surgery 7: 1.
3. Kolm I, Di Stefani A, Hofmann-Wellenhof R, Fink-Puches R, Wolf IH, et al. (2006) Dermoscopy patterns of halo nevi. Arch Dermatol 142: 1627-1632.
4. Misra RS, Iyengar B (1991) Halo Nevus - A Clinical Pathological Evaluation. Ind. J. Derm Ven Lep 57: 210-213.
5. Mackie RM (2004) Disorders of the cutaneous melanocyte: halo nevus. Rook's Textbook of Dermatology. (7thedn). Blackwell Scientific Publications, Oxford, England. 1-39
6. Patrizi A, Neri I, Sabattini E, Rizzoli L, Misciali C (2005) Unusual inflammatory and hyperkeratotic halo naevus in children. Br J Dermatol 152: 357-360.
7. Rados J, Pastar Z, LipozenciÄ‡ J, IliÄ‡ I, Stulhofer Buzina D (2009) Halo phenomenon with regression of acquired melanocytic nevi: a case report. Acta Dermatovenerol Croat 17: 139-143.
8. Mooney MA, Barr RJ, Buxton MG (1995) Halo nevus or halo phenomenon? A study of 142 cases. J Cutan Pathol 22: 342-348.
9. Aouthmany M, Weinstein M, Zirwas MJ, Brodell RT (2012) The natural history of halo nevi: a retrospective case series. J Am Acad Dermatol 67: 582-586.
10. Harvell JD, Meehan SA, LeBoit PE (1997) Spitz's nevi with halo reaction: a histopathologic study of 17 cases. J Cutan Pathol 24: 611-619.
11. de Vijlder HC, Westerhof W, Schreuder GM, de Lange P, Claas FH (2004) Difference in pathogenesis between vitiligo vulgaris and halo nevi associated with vitiligo is supported by an HLA association study. Pigment Cell Res 17: 270-274.

12. Brandt O, Christophers E, Fölster-Holst R (2005) Halo dermatitis followed by the development of vitiligo associated with Sutton's nevi. J Am Acad Dermatol 52: S101-104.

13. Patrizi A, Bentivogli M, Raone B, Dondi A, Tabanelli M, et al. (2013) Association of halo nevus/i and vitiligo in childhood: a retrospective observational study. J Eur Acad Dermatol Venereol 27: e148-152.

14. Bennett C, Copeman PW (1979) Melanocyte mutation in halo naevus and malignant melanoma? Br J Dermatol 100: 423-426.

15. Albert DM, Todes-Taylor N, Wagoner M, Nordlund JJ, Lerner AB (1982) Vitiligo or halo nevi occurring in two patients with choroidal melanoma. Arch Dermatol 118: 34-36.

16. Epstein WL, Sagebeil R, Spitler L, Wybran J, Reed WB, et al. (1973) Halo nevi and melanoma. JAMA 225: 373-377.

17. Latuska R, Sinha N, Shields CL (2011) Halo Nevus of the Choroid: An Innocent Bystander Retina Today, Ocular Oncology, Oncology Case Reports.

18. Shields CL, Maktabi AM, Jahnle E, Mashayekhi A, Lally SE, et al. (2010) Halo nevus of the choroid in 150 patients: the 2010 Henry van Dyke Lecture. Arch Ophthalmol 128: 859-864.

19. Zeff RA, Freitag A, Grin CM, Grant-Kels JM (1997) The immune response in halo nevi. J Am Acad Dermatol 37: 620-624.

20. Bayer-Garner IB, Ivan D, Schwartz MR, Tschen JA (2004) The immunopathology of regression in benign lichenoid keratosis, keratoacanthoma and halo nevus. Clin Med Res 2: 89-97.

21. Weedon D (2002) Skin pathology. (2ndedtn). Edinburgh, London, New York, , Philadelphia, St.Louis, Sydney, Toronto: Churchill Livingstone;. pp. 810-811.

22. Mikel UV (1994) Advanced Laboratory Methods in Histology and Pathology. American Registry of Pathology, Armed Forces Institute of Pathology, Washington DC, USA

23. Pearse AGE (1985) Histochemistry theoretical and applied. Vol II: Analytical Technology. Churchill Livingstone, London. Pp 611-674.

24. Prophet ED, Mills B, Arrington JB, Sobin LH, (1994) Laboratory Methods in Histotechnology. American Registry of Pathology, Armed Forces Institute of Pathology, Washington DC.

25. Iyengar B, Banerjee B, Chandra K (1976) The morphogenesis of melanotic lesions. Indian J Cancer 13: 143-148.

26. Iyengar B, Banerjee B, Chandra K (1976) Pigment production in melanotic lesions of the skin. Indian J Cancer 13: 238-242.

27. Fritsch P (2004) Dermatologie und Venerologie. Grundlagen, Klinik und Atlas. (2ndedtn). Springer, Berlin, Germany. 627

28. Usatine RP (1999) Skin lesions with white rings. West J Med 171: 8-9.

29. Herd RM, Hunter JA (1998) Familial halo naevi. Clin Exp Dermatol 23: 68-69.

30. Huynh PM, Lazova R, Bolognia JL (2001) Unusual halo nevi--darkening rather than lightening of the central nevus. Dermatology 202: 324-327.

31. Tokura Y, Yamanaka K, Wakita H, Kurokawa S, Horiguchi D, et al. (1994) Halo congenital nevus undergoing spontaneous regression. Involvement of T-cell immunity in involution and presence of circulating anti-nevus cell IgM antibodies. Arch Dermatol 130: 1036-1041.

32. Mc Kee P, Calonje E, Granter SR (2005) Pathology of the skin with clinical correlation. (3rdedtn). Elsevier Mosby, Boston. pp.1266-8.

33. Iyengar B (2014) Tumor Vascular Interaction in Melanomas and Neurogenesis A Review Pigmentary Disorders, 1: 2.