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# Hypopigmented mycosis fungoides clinical, histopathological and immunohistochemical study

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Normal human skin colour is dependent on haemoglobin, carotenoids and melanin pigment. Of these, melanin is a major determinant of differences in skin colour. Melanocytes are the cells that possess the metabolic machinery for the synthesis of melanin. They locate in the basal layer of the epidermis. The cell body of the melanocyte sites in a specialized region of basal lamina, its dendrites come into contact with keratinocytes as far away as the mid stratum spinosum. This association of melanocyte with approximately 30-40 surrounding keratinocytes has been called the epidermal melanin unit. In a healthy skin, there is a molecular microenvironment that favours the survival of the melanocyte and regulates its function. In particular, keratinocytes can synthesize and secrete several cytokines that have both stimulatory and inhibitory action on melanocyte activity, such as TNF- $\alpha$ . Thus, an alteration of this microenvironment constituted by cytokines can explain the disappearance of the melanocyte in various hypopigmented disorders. Cytokines are structurally related polypeptides or glycoproteins that exert their effects by binding to specific receptors on the cell membrane, followed by activation of different signaling pathways, resulting in various immunomodulatory and growth regulatory effects. Cytokines include : interleukins, interferons, colony stimulating factors, tumour necrosis factors, growth factors and chemokines. Tumour necrosis factor (TNF) is a cytokine with multiple biological activities. The TNF family includes : TNF- $\alpha$  (cachectin), TNF- $\beta$  (lymphotoxin), Fas ligand (FasL), CD27L, CD30L and CD40L. TNF- $\alpha$  is produced by many cell types including activated monocytes, macrophages and keratinocytes. It is involved in various biologic activities in many tissues through its two distinct cell surface receptors; TNF-RI and TNF-RII. These include : immunoinflammatory effects, metabolic effects, role in infections, apoptotic effects, antitumour effect and melanogenesis. TNF- $\alpha$  has an inhibitory effect on melanogenesis. This inhibitory effect could be explained by decreased intracellular levels of tyrosinase and tyrosinase - related protein 1 (TRP-1) (enzymes involved in melanin synthesis) as well as inhibition of melanocytes proliferation, or induction of melanocytes apoptosis. This study was conducted to study the role of one of the keratinocyte - derived cytokines, tumour necrosis factor -  $\alpha$  (TNF- $\alpha$ ) in the pathogenesis of hypopigmented mycosis fungoides, as well as, two other hypopigmented disorders; namely vitiligo, and hypopigmented type of tinea versicolour. Twenty nine patients,

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divided into 3 groups (9 hypopigmented MF, 10 vitiligo, 10 hypopigmented TV) and 10 normal healthy controls were included in this study. A 4- mm punch skin biopsy was taken from lesional skin of every patient as well as from the normal skin of each individual in the control group. Sections 4 – mm thickness were mounted on positive charged slides for immunohistochemical staining for TNF- $\alpha$  expression using Avidin – Biotin complex technique. The expression of TNF- $\alpha$  in lesional skin of different groups was significantly higher than in control skin. One important implication raised by our findings. In normal skin, TNF- $\alpha$  expression was on basal keratinocytes, showing focal density and weak staining intensity in almost all cases (100%) as shown in (fig. 18,19). In group I (hypopigmented MF), TNF- $\alpha$  expression was diffuse and of strong staining intensity in 77.8% of patients, as shown in (fig. 20,21). In group II (vitiligo), TNF- $\alpha$  expression was diffuse and of strong staining intensity in 80% of patients, as shown in (fig. 23,24). In group III (hypopigmented TV), TNF- $\alpha$  expression was diffuse and of moderate staining intensity in 80% of patients, as shown in (fig. 25,26). All 3 studied hypopigmented disorders were found to share the same change in cutaneous microenvironment with increased TNF- $\alpha$  expression (a normal inhibitor of human melanocyte proliferation and melanogenesis). Thus, this change in cutaneous microenvironment may explain the pigment loss in these three diseased groups, as well as other hypopigmented disorders to be further investigated. Suppression of these cytokines or their substitution with the new biological therapies may be associated with repigmentation of these hypopigmented disorders.

**RECOMMENDATIONS**

Further studies are needed to clarify:

- The hypothesis that cytotoxic CD8+ T-cell in hypopigmented MF have an additional effect on excess production of TNF- $\alpha$ .
- The possible inhibitory effect of TNF- $\alpha$  on keratinocyte production of other cytokines which may affect melanocytes in vitiligo.
- Suppression of TNF- $\alpha$  by new biological therapy (TNF- $\alpha$  blocker) may be associated with repigmentation of vitiligo.
- Comparison between TNF- $\alpha$  level in hypopigmented TV as compared with hyperpigmented type.
- Comparison between TNF- $\alpha$  level in hypopigmented MF as compared with classic MF.
- The role of other cytokines which constitute the cutaneous micro- environment in the pigment loss in hypopigmented disorders.