Case Report

SHABBIR SYNDROME: A CASE REPORT AND REVIEW OF ITS GENETIC BASIS

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Abstract: Shabbir syndrome is a rare, progressive, multisystem disorder with an autosomal recessive pattern of inheritance. It mainly afflicts children from Punjabi Muslim families of Pakistan and India. The genetic anomaly has been mapped as a mutation in LAMA3 gene on chromosome 18q11.2.

A 17-year-old male presented to us with history of recurrent skin ulcers, nail dystrophy and laryngeal obstruction. Fresh ulcers, older crusted ulcers and cicatrisation in his head and neck area were strikingly obvious. Skin biopsy was submitted and revealed characteristic exuberant granulation tissue with a mixed acute and chronic cell infiltrate. Other features are also described.

LAMA3 gene is responsible for the production of laminin α3 which is one of the three components of laminin, a heterotrimer. Laminin is an important part of the cell membrane and extends into the dermis. Its presence is a signal to the dermis that the basement membrane is intact and the production of granulation tissue is kept in check. Abnormal lamininfails to do it resulting in excessive, undesirable granulation tissue production. Understanding this feedback mechanism may enable us to control the production of granulation tissue in Shabbir syndrome as well as other diseases like rheumatoid arthritis and chronic venous ulcers.

Keywords: Shabbir syndrome, laryngo-onycho-cutaneous syndrome (LOCs), Laryngeal and ocular granulation tissue in children from the Indian subcontinent (LOGIC syndrome), granulation tissue.

Introduction

In 1986, Professor Syed Ghulam Shabbir et al published a series of 22 children from 12 families who had presented with chronic skin ulcers, hoarseness of voice and dystrophic changes in nails. The disorder was named laryngo-onycho-cutaneous syndrome or LOCS but it soon came to be known as Shabbir syndrome.[1] This was soon followed by reports from elsewhere which elaborated further on this strange disorder which consistently seemed to affect children from Muslim families from Punjab province in Pakistan and India. The parents were consanguineous in the vast majority of cases and more than one offspring was seen to be affected frequently. These observations hinted it to be a disease with autosomal recessive inheritance.[2,3] Eyes were described to be another target organ of the disease which showed uncontrolled proliferation of granulation tissue in dermal and submucosal areas.Several patients showed dental abnormalities as well.[4]It was proposed that it should be called LOGIC syndrome, an acronym for Laryngeal and Ocular Granulationtissue in Children from the Indian subcontinent.[2,3,5]

The disease manifested itself in the neonatal period or infancy. It varied in its intensity and was fatal in a large proportion of cases. The major cause of death was laryngeal obstruction followed by infection in skin ulcers. Blindness was also frequently reported.[6] The disease was found to be frustratingly refractory to the treatment modalities available at the time, for example, antibiotics, anti tuberculous drugs, anti leprosy drugs, steroids etc. Intriguing as it is, it remains a rare disease with fewer than 50 cases having been reported so far.[5,7]

A case of Shabbir syndrome was recently encountered and is presented here along with a brief literature review.

Case Report

A 17-year-old male presented to Department of Plastic Surgery,Jinnah Hospital Lahore. He gave history of chronic ulcers all over his body since birth.He also gave history of recurrent respiratory infections, difficulty in speech since childhood. He had an episode of respiratory obstruction one year back which he had been relieved by laser 2 years ago. He gave no family history of similar ailments. He had 3 siblings who were all normal. His parents were first cousins.

He had a hoarse voice. There was widespread ulceration of skin all over his head and neck area. It was more marked on his face where fresh ulcers, older crusted ulcers and cicatrisation were striking **(Fig 1).**

There was pronounced involvement of left lower lid and conjunctiva **(Fig 2).** There was marked nail dystrophy involving both hands (Fig 3). Hair growth was unaffected (Fig 1).Rest of his body was spared though he gave history of occasional ulceration elsewhere **(Table 1).**[8]

Table-1: The major phenotypic manifestations of Shabbir syndrome, their frequency, where determined, and their presence and severity in our patient.[8]

S. No.	Description	Frequency	Whether present in our pt.
1	skin ulcer	Hallmark (90%)	++
2	abnormal pigmentation of the oral mucosa	Hallmark (90%)	+/-
4	abnormality of the toenails	Hallmark (90%)	++
3	opacification of the corneal stroma	Hallmark (90%)	-
5	tracheoesophageal fistula	Hallmark (90%)	-
6	Anonychia	Hallmark (90%)	-
7	abnormality of the voice	Hallmark (90%)	++
8	abnormality of the fingernails	Hallmark (90%)	++
9	abnormality of dental enamel	Hallmark (90%)	++
10	recurrent respiratory infections	Typical (50%)	++
11	respiratory insufficiency	Typical (50%)	++
12	recurrent loss of toenails and fingernails	Not determined	++
13	Hoarse cry	Not determined	+/-
14	Weak cry	Not determined	+/-
15	Amelogensesis imperfecta	Not determined	++
16	Abnormmality of the eye	Not determined	+

The Department of Plastic Surgery planned reconstruction of his left lower lid.

Two of his skin lesions were sampled and submitted to Department of Pathology, Allama Iqbal Medical College, Lahore. Gross examination of these revealed two tiny grey white fragments measuring 0.3x0.2x0.2 cm in aggregate. One of them was partially skin covered. Microscopic examination of biopsy revealed two fragments mostly comprised of granulation tissue **(Fig 4 and 5)**. One of these had a partial covering of epidermis. This showed thinning over most areas and a central area of ulceration **(Fig 4)**. Both fragments contained heavy infiltration by a mixed but mostly chronic inflammatory infiltrate **(Fig 4 and 5).** Overall the findings were quite nonspecific.

Shabbir syndrome is a rare, progressive, multisystem disease with an autosomal recessive pattern of inheritance.[9]There have been steady, incremental advances in our understanding of its genetic basis. Some of these are also shedding light on mechanisms underlying control of granulation tissue formation and the complex interactions between keratinocytes and underlying dermis. The initial grim picture is being replaced by a more optimistic one.

The genetic defect has been localized to a region on chromosome 18q11.2. This region includes the laminin alpha3 (*LAMA3*) gene. The protein coded by this gene is the alpha 3 subunit of laminin 332 (formerly called laminin 5). More specifically, a frameshift mutation coded as 151insG, has been identified. A frameshift mutation is one that involves insertion or deletion, in the DNA sequence, of a group of nucleotides the number of which is not divisible by three. As is well known, nucleotides work in groups of three; each group being called a codon which encodes for one amino acid. The result of such insertion or deletion is that the entire frame of transcription is altered producing proteins grossly divergent from the ones intended. This also affects the "stop codons" and so the resulting protein is either abnormally long or abnormally short. In case of Shabbir syndrome the new protein is shorter by 226 amino acids at its N terminal. This abnormal, truncated protein is obviously unable to perform its required function. LAMA3α is secreted by basal keratinocytes, joins β and γ subunits to form laminin332, and gets incorporated into the basement membrane whereits N terminal negatively regulates granulation tissue formation by the underlying mesenchyme. Its presence signals to the underlying mesenchyme that the basement membrane is intact. Loss of this feedback triggers an unchecked proliferation of granulation tissue which is the hallmark of this disease. This also explains why there is greater proliferation of granulation tissue at sites where there is even mild but repetitive trauma such as the skin, vocal cords, eyes and nails. This theory is called the Keratinocyte-Mesenchymal miscommunication theory.[9,10,11]

Shabbir syndrome shares some features with epidermolysis bullosa and has been classified as a subtype of junctional epidermolysis bullosa.[6,12,13], This implies that these disorders might be amenable to similar modes of treatment.[14] Since its original description it was thought to afflict Punjabi, Muslim families only, but recently cases have been reported from elsewhere like Iran. These cases are clinically indistinguishable from Shabbir syndrome though the genetic anomaly is slightly different.[13,15]

The diagnosis is usually straightforward. A list of

manifestations along with their frequencies has been compiled. Our patient suffered from most of the expected predicaments **(Table 1, Fig 1-3**).[8]

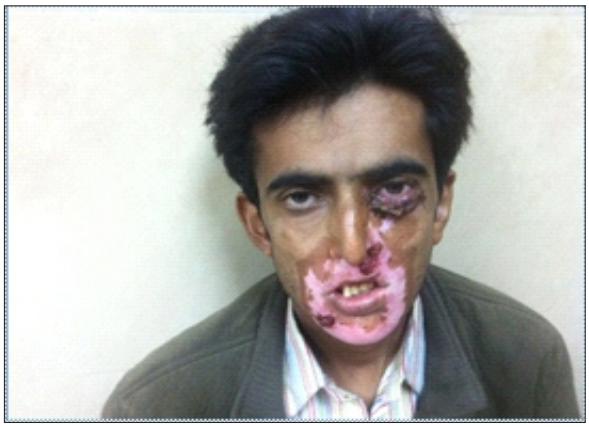

Fig-1: Photograph of patient, fresh ulcers, crusted ulcers and cicatrisation are strikingly obvious.

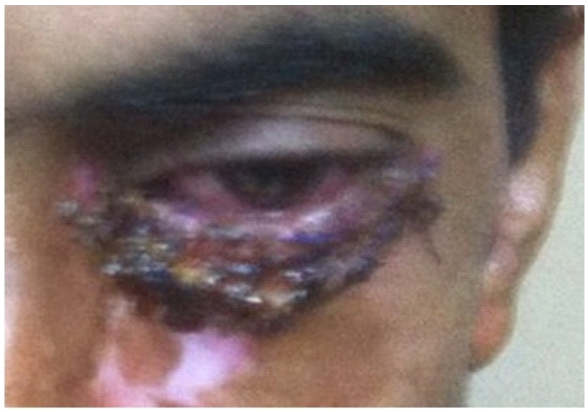

Fig-2: There is pronounced involvement of lids and conjunctiva.

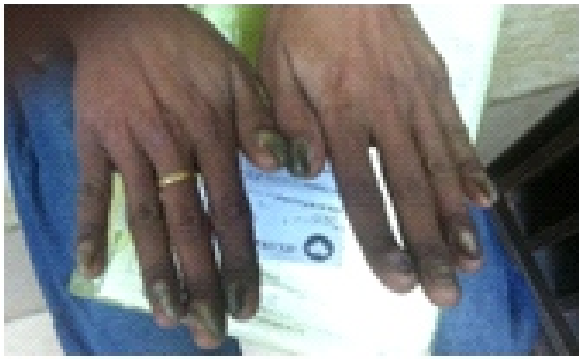

Fig-3: There is marked nail dystrophy involving both hands.

Microscopic findings are quite nonspecific and only reveal masses of granulation tissue with acute and chronic inflammatory cells. Similar features were seen in our patient **(Fig 4 and 5).**[5]

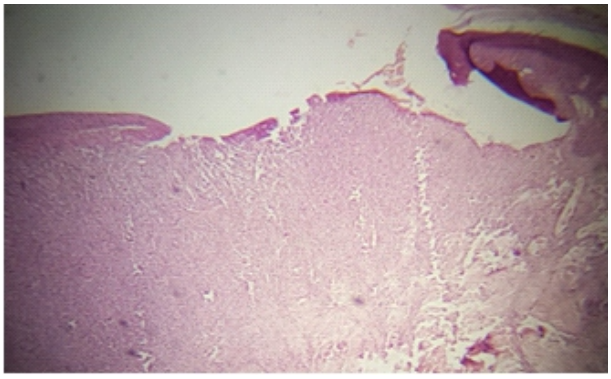

Fig-4: Photomicrograph showing exuberant granulation tissue in the dermis. Epidermis shows thinning and central ulceration. (H & E, x200).

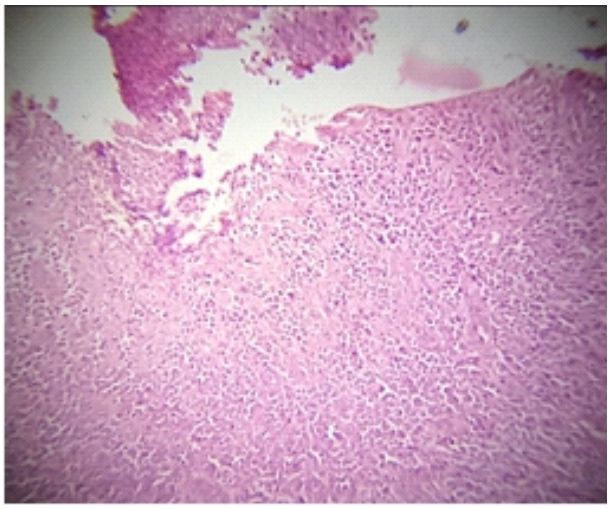

Fig-5: High powered view depicting granulation tissue heavily infiltrated by a mixed acute and chronic inflammatory infiltrate. (H & E, x400).

Numerous drugs with different modes of action have been used with variable success. These include thalidomide, an immunomodulatory drug; cyclosporine, an immunosuppressant; topical 5FU, a cytotoxic agent; and systemic steroids.[10,16]

Laryngeal obstruction is one of the feared complications of Shabbir syndrome and along with skin infections accounts for most of the premature deaths in these patients. Laser therapy has been reported to be partially successful in relieving laryngeal obstruction. [5,14]Our patient was also benefitted from it, and has not had a relapse in two years.

Other, newer methods are being explored to manage the various complications. Dryness of eyes and conjunctival ulcers are major contributors to

blindness. Recent reports describing amniotic membrane transplantation are encouraging. It is supposed to act by providing mechanical protection as well as delivering healthy laminin 332 to the tissues, temporarily compensating for their deficiency of this important factor. Conjunctival and corneal stem cell transplantation is also being considered but would require long term immunosuppression. Buccal and nasal mucus membrane autografts are another option in patients where these are spared of disease.[10] One rather drastic, multistage procedure called osteo-odonto-keratoprosthesis (OOKP), has recently been tried in a patient of Shabbir syndrome. This process is designed to help patients with the most severe corneal and ocular surface problems while the posterior segment is intact. In various steps the front area is debrided and then a new anterior surface built by combing tissues from the patient's tooth, its surrounding bone and buccal mucosa.[7]

Gene replacement therapy is another avenue to be explored. It would involve ex vivo, retroviral transduction of autologous epithelial cells. These could then be reintroduced to effected areas. Another approach being considered is production of recombinant laminin 332. This would involve the insertion, within bacterial plasmids, of DNA sequences responsible for producing laminin 332. As these bacteria divide and multiply, they can be used as factories for the production of this protein. The major impediment to this approach is the large size of laminin 332 which, as already stated, is a heterotrimer. This huge molecule would find it difficult to traverse epithelial layers to reach the basement membrane where its action is required. So the current aim is to produce a smaller recombinant peptide analogue that would replace the 226 amino acid missing portion of laminin3α already discussed. Finally, the ultimate accomplishment would be development of a transgenic mouse model of Shabbir syndrome that would allow testing the efficacy of these methods.[10]

In conclusion, molecular basis of Shabbir syndrome is an area of active study, facts have emerged slowly like peeling away the layers of an onion. The following interesting observations should be taken note of:

a) Determination of the precise gene defect of any inherited disease would be the first step towards its management.[9]

b) Various, apparently dissimilar, diseases may share genetic aberrations making it possible to find common treatment modalities, for example, LAMA3α defects have been described in patients of junctional epidermolysis bullosa, German atopic dermatitis and amyotrophic lateral sclerosis.[12,17]

c) Excessive and undesirable granulation tissue formation is a problem in several more common conditions such as rheumatoid arthritis, chronic venous ulcers, transplant surgery etc. A fuller understanding of the control mechanisms could lead to the identification of novel targets for therapeutic interventions in these conditions as well.[9]

d) Diligent follow up of reported patients has indicated that those who survive into the second decade generally fare better.[11] We hope this will be case in our patient too.

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Answer Picture Quiz

Aberrant right subclavian artery (ARSA)

ARSA is the most common aortic arch anomaly and aneurysmal dilatation of proximal portion of aberrant right subclavian artery is common and referred to as Kommerell diverticulum which appears as bulbous enlargement of proximal subclavian artery at its origin from aortic arch, posterior to oesophagus.