Superimposed mosaicism in tuberous sclerosis complex: a key to understanding all of the manifold manifestations?

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Abstract
In patients with tuberous sclerosis, we can today distinguish between two different categories of segmental mosaicism. The well-known simple segmental mosaicism is characterized by a unilateral or otherwise localized arrangement of the ordinary lesions of the disorder, reflecting heterozygosity for an early postzygotic new mutation. By contrast, superimposed mosaicism is defined by a pronounced segmental involvement in a patient with ordinary non-segmental lesions of the same disorder, resulting in a heterozygous embryo from loss of the corresponding wild-type allele that occurred at a very early developmental stage. So far, the second category has been called ‘type 2 segmental mosaicism’, but here we propose the short and unambiguous term ‘superimposed mosaicism’. In order to render physicians familiar with the manifold manifestations of this category as noted in tuberous sclerosis, we review the following clinical designations under which cases suggesting superimposed mosaicism have been published: forehead plaque; shagreen patch; fibrous cephalic plaque; fibromatous lesion of the scalp; folliculocystic and collagen hamartoma; segmental hypomelanosis; congenital segmental lymphedema; and segmental ‘diffuse’ lipomatosis. Molecular corroboration of this genetic concept has been provided in a case of forehead plaque and in a child with shagreen patch. – Extracutaneous manifestations suggesting superimposed mosaicism include columnar tuberous brain defects; ‘radial migration lines’ or ‘cerebral white matter migration lines’ as noted by brain imaging; linear hamartomatous lesions of the tongue; fibrous dysplasia of bones including macroactodacy; and unilateral overgrowth of an arm or leg. – Remarkably, superimposed mosaicism appears to occur in tuberous sclerosis far more frequently than simple segmental mosaicism.

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Introduction
Tuberous sclerosis complex (TSC) is an autosomal dominant disorder characterized by diversiform skin lesions and hamartomas of brain, heart, lungs and kidneys. When we consider the various clinical features of TSC, we should realize that in this autosomal dominant trait there is, according to present knowledge, no monoallelic heterozygous manifestation.1–4 Hence, all lesions of TSC are biallelic, reflecting mosaicism that originates from loss of the corresponding wild-type allele,5–8 which is in contrast to the monoallelic manifestation as customarily admitted in autosomal dominant disorders such as epidermolytic ichthyosis of Brocq. As with other genuinely biallelic cutaneous autosomal dominant disorders, mosaic TSC lesions are known to occur, so far, in three different forms (Fig. 1).9 Firstly, disseminated mosaicism is noted in ‘classic’ TSC being characterized by a non-segmental arrangement of facial angiofibromas,1 ash-leaf macules,2 cerebral tubers,3 subependymal giant cell astrocytomas4–7 and renal angiomyolipomas.5,8 The second-hits take place during most of the intrauterine time or the entire postnatal life. The term ‘disseminated mosaicism’ means that the lesions do not follow any of the known patterns of segmental mosaicism.9 Secondly, simple segmental mosaicism occurs in the form of unilateral or otherwise segmental arrangement of the usual lesions such as angiofibromas, ash-leaf macules, Koenen tumours or cerebral tubers.10,11 This presentation is due to a postzygotic new mutation arising, in an embryo with two wild-type alleles, at a very early developmental stage. It may lead to simultaneous gonadal mosaicism, which implies a slightly
increased risk for these individuals to transmit the disorder to the next generation in the form of non-segmental TSC. Thirdly, *superimposed mosaicism* is characterized by the presence of a pronounced segmental involvement in addition to ‘classic’, non-segmental TSC. This is a result of loss of the corresponding wild-type allele occurring during the first stages of embryogenesis.9,12

Until today, however, confusion prevails regarding the mosaic manifestations of TSC because many authors do not discriminate between the two distinct categories, simple segmental vs. superimposed mosaicism.11,13–15 Therefore, the purpose of the present review is to render readers familiar with pronounced mosaic cutaneous or extracutaneous lesions being superimposed on the ordinary, non-segmental phenotype. So far, this distinct type of mosaicism has been described as ‘type 2 segmental manifestation’12 or ‘type 2 segmental mosaicism’.9 However, because all superimposed mosaic lesions of autosomal dominant skin disorders including TSC display a segmental arrangement, the short term ‘superimposed mosaicism’ is proposed here as an appropriate designation.

**Clinical features of suggesting superimposed mosaicism in TSC**

These manifold segmental manifestations as noted in TSC have been described under various names. In fact, all of them can be subsumed under a single genetic term, superimposed mosaicism. With this concept in mind, the diverse pertinent designations will be considered in the following paragraphs.

**Shagreen patch**

Segmental patches of increased fibrous tissue, often associated with cobblestone-like surface, are a typical feature of TSC. These patches tend to involve the lumbar region (Fig. 2),16–18 but are also noted in other areas of the body. All sizeable patches of this kind can be best explained as superimposed mosaic lesions.

**Forehead plaque**

In 1987, Fryer et al.19 proposed this term for a lateralized, linear fibrous hamartoma involving the forehead (Fig. 3). Today, it is taken as a major diagnostic feature of TSC,20,21 but in principle it can be taken as a shagreen patch in a particular location.

**Fibrous cephalic plaque**

This name is presently used to describe the forehead plaque and similar segmental lesions involving other parts of the head including the scalp (Fig. 4).20,22–24 On the other hand, small papules or nodules of similar hamartomatous tissue22 reflect most likely disseminated mosaicism.9

**Fibromatous lesion of the scalp**

Under this term, Baykal et al.25 have documented large, soft lesions of the scalp showing scarce or no hair growth (Fig. 5). This is another name for fibrous cephalic plaques. Of note, the authors included small papular or nodular lesions that can be categorized as examples of disseminated mosaicism.9
Folliculocystic and collagen hamartoma

In 2012, this name was proposed by Torrelo et al.26 to delineate segmental lesions consisting of large infiltrated, tumour-like plaques that may involve all regions of the body. They are present at birth, and in time, they develop multiple comedones and cysts containing a draining keratinous or purulent material (Fig. 6).

Histopathologically, perifollicular fibrosis is a typical feature of this collagen hamartoma. The authors assumed that ‘at least some cases represent a type 2 segmental manifestation of TSC, superimposed on the usual features of the autosomal dominant disorder’.27 In the light of further publications on folliculocystic and collagen hamartoma,28–31 we can today conclude that all cases of this particular skin lesion reflect superimposed mosaicism. The disorder has preponderantly been found in male patients.26 At present, the male-to-female ratio is 8 : 2. – Under the term ‘fibrous hamartoma of infancy’, Han et al.32 described a 12 × 6.5 cm tumour of soft tissue that had rapidly grown on the abdominal wall of a 4-year-old boy with TSC. CT images and photographs of the excised tumour clearly show that this was a typical case of folliculocystic and collagen hamartoma avant la lettre. At the surface of the tumour, many comedones and a large follicular cyst were documented.

Segmental hypomelanosis

On rare occasions, patients with TSC may show segmental areas of hypomelanosis which can best be explained as a superimposed mosaic manifestation of the ordinary disseminated ash-leaf spots. Conspicuous examples have inadvertently been documented by Ortonne et al.33 and Jindal et al.34 Moreover, in a 9-month-old boy with bilateral disseminated ash-leaf spots, cerebro tubers and seizures, Selvaraj et al.35 described an unusually large ‘ash-leaf macule’ involving his left periocular region with ipsilateral cataract (Fig. 7). After vitrectomy, examination of the retina revealed two astrocytic hamartomas, whereas his right eye was found to be unaffected. This colocalization of cutaneous and intraocular features may likewise represent an example of superimposed mosaicism. In another case, Malissen et al.36 have shown that such large hypopigmented lesions can successfully be treated with topical sirolimus cream.
Congenital segmental lymphedema
So far, this anomaly has been documented in at least 13 children with TSC. Clinical features suggesting superimposed mosaicism include the presence at birth and strict lateralization of the disorder, ipsilateral aplasia of iliac or inguinal lymph nodes and the association with multiple aneurysms of ipsilateral large arteries.

Segmental ‘diffuse’ lipomatosis
This abnormality is characterized by hamartomatous growth of fatty tissue infiltrating the skin, subcutaneous tissue and muscles. The word ‘diffuse’ is ambiguous because all reported cases show a segmental arrangement. Another conspicuous example was photographically documented by Klein and Bar. In a 15-year-old boy, the right buttock and leg were diffusely enlarged without any lymphedema. A xeroradiograph showed focal lobular infiltrates of fatty tissue within the muscles. A skin biopsy showed lobules of fatty tissue infiltrating the reticular dermis.

Extracutaneous manifestations of superimposed mosaicism
The extracutaneous features of superimposed mosaicism in TSC and other autosomal dominant skin disorders have recently been reviewed. Contrasting with disseminated cerebral tubers, columnar cerebral defects radiating to the cortex suggest superimposed mosaicism (Fig. 10). Notably, the terms ‘radial migration lines’ or ‘cerebral white matter migration lines’ appear to be consistent with this genetic concept. Other extracutaneous features suggesting superimposed mosaicism include linear hamartomatous lesions of the tongue, segmental fibrous dysplasia of bones, including macrodactyly (Fig. 13) and unilateral occurrence of multiple arterial aneurysms in childhood. Moreover, unilateral overgrowth of a limb and ‘diffuse’ lipomatosis involving a leg or the thoracic wall could also be categorized among the extracutaneous manifestations of this particular form of mosaicism. – So far, the question cannot be settled whether some cases of unilateral giant renal angiomyolipoma may also reflect superimposed mosaicism, because a bilateral involvement is rather often reported.

Conclusive remarks
In TSC, molecular corroboration of this concept has been provided, so far, in two cases only. Tybusczy et al. documented compound heterozygosity for TSC2 mutations in a shagreen patch and in a forehead plaque of another patient. We should bear in mind, however, that in this disorder, the significance of such molecular analysis is rather limited because today we know that all of the disseminated, non-segmental lesions of TSC do likewise originate from second-hit events resulting in allelic loss, including facial angiofibromas, ash-leaf macules, cerebral tubers, subependymal giant cell astrocytomas and renal angiomyolipomas. And angiofibromas of patients with simple segmental TSC were also found to harbour biallelic
mutations.\textsuperscript{11} Hence, why should superimposed mosaic TSC lesions not result from the same genetic mechanism? The crucial difference is the point in time when the event of biallelic loss occurs. In superimposed mosaicism, it must happen rather early, during the first stages of embryonic development, whereas the ‘classic’ TSC lesions reflecting disseminated mosaicism can develop later during intrauterine or the entire postnatal life.

In the past, a case of superimposed mosaic TSC has erroneously been taken as a ‘forme fruste of Bourneville tuberous sclerosis’ by Garcia-Muret \textit{et al}.\textsuperscript{66} who described unilateral facial angiofibromas in an infant who later developed less pronounced contralateral facial lesions as well as a renal angiomyolipoma.\textsuperscript{27,67} Subsequently, this case was mistaken by two groups as an example of simple segmental TSC.\textsuperscript{13,14} Others have explained large shagreen patches as representing simple segmental mosaicism.\textsuperscript{68}

Notably, superimposed mosaicism tends to occur in TSC far more often than simple segmental mosaicism.\textsuperscript{69} Such high degree of proclivity to develop superimposed mosaicism is also found in some other autosomal dominant skin disorders such as glomangiomatosis and the various types of porokeratosis.\textsuperscript{69}

When elaborating this concept, it is not our intention to abolish the traditional names of TSC lesions as itemized above. Rather, we want to deepen the understanding of TSC and

\textbf{Figure 10} Columnar cerebral tuberous defect in tuberous sclerosis complex, suggesting superimposed mosaicism.\textsuperscript{59} (Reproduced with permission from Springer Nature, New York, USA).

\textbf{Figure 11} Radial migration line (arrow) as a tuberous sclerosis complex-specific brain abnormality.\textsuperscript{51} (Reproduced with permission from Springer Nature, New York, USA).

\textbf{Figure 12} Linear hamartoma of the tongue in a 17-year-old patient with tuberous sclerosis.\textsuperscript{52} (Reproduced with permission from BMJ Publishing Group Ltd., UK).

\textbf{Figure 13} (a/b) Macroductyly in an 11-year-old boy with tuberous sclerosis.\textsuperscript{57} (a) Clinical appearance; (b) X-ray shows irregular periosteal new bone formation (arrows) and cortical cysts (arrowhead). (Reproduced with permission from Springer Nature, New York, USA).
stimulate further research, by accumulating clinical examples suggesting superimposed mosaicism.

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