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Case report

Adhesive capsulitis in a patient affected by KBG Syndrome

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Abstract. *Background and Case presentation:* KBG syndrome is a multiple congenital anomaly syndrome with variable presentation. Many physical anomalies also affect the orthopaedic field. We present a case of a young woman with diagnosis of KBG syndrome that is also affected by joint stiffness and adhesive capsulitis to the shoulders. *Discussion:* Many other cases have been reported to present joint stiffness and formation of keloids. Adhesive capsulitis is known to be related to autoimmune pathologies and endocrinological disorders. KBG syndrome is caused by heterozygous mutation in ANKRD11 gene and few patients with hypermobility of the joints have also been reported. *Conclusions:* The KBG syndrome might present a risk factor for adhesive capsulitis of the shoulder and joint stiffness in general. Moreover, the tendency to the formation of keloids and sporadic cases of hypermobility might suggest a connective tissue involvement in different gene deletions. (www.actabiomedica.it)

Key words: KBG syndrome, ANKRD11, Rare Diseases, Adhesive Capsulitis, Shoulder.

Case

A patient aged 38 years referred right shoulder pain associated with severe stiffness. In 2016, at the age of 34, she had seen other specialists for a left shoulder pain with mild reduction of range of motion. No other specific evidence was enlightened at the clinical evaluation in 2016 and the symptoms were solved after physiotherapy. She also referred recurrent pain and stiffness to fingers and hands. No other diagnosis was made at the time. However, due to ongoing uncertainty regarding a possible hereditary connective tissue disorder, the patient had been under the care of a Clinical Geneticist since 2014. In 2016, she underwent molecular genetic tests, such as array-CGH and FLNA gene analysis, that gave negative results. After few years, she returned to the Geneticist and whole exome sequencing (WES) analysis, performed on DNA extracted from peripheral blood, identified the presence of c.2409_2412del (p.Glu805Argfs*57) variant in ANKRD11 gene in heterozygosis. This variant is associated with KBG syndrome (MIM611192). The patient received the diagnosis of KBG syndrome in 2019, approximately 6 months before she had the shoulder evaluation. During the last 5 years she has reported recurrent osteo-muscular joints pain and associated episodic stiffness. These symptoms mainly affected the hands and were autonomously treated by the patient with NSAIDs. No specific history was reported about her consanguineous.

On examining her, she had several distinctive facial features: large prominent ears, macrodontia, anteverted nares, hypertelorism, and triangular face. Brachydactyly was present and associated with clinodactyly in the hands. A previous MRI of the spine showed alterations of probable congenital origin.

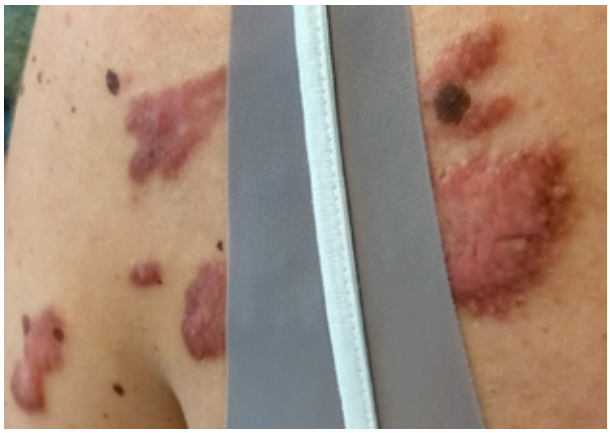

Figure 1. Multiple inflammatory keloids

Pseudo fusion of C5-C6, lumbosacral transitional vertebrae, anterior wedge deformity of D6-D7, increased dorsal kyphosis, and unspecific alterations associated to multiple disc herniations were found. Amaurosis fugax was also reported by the patient and was currently under investigation as well as a mitral valve prolapse with a mild insufficiency which had been diagnosed in 2002. A neuropsychomotor developmental delay and a very mild intellectual impairment as an adult was also referred. A brain MRI was performed at age 8 years and an olivopontocerebellar atrophy was evidenced, then a second MRI at age 30 years was performed. A first evaluation described a cerebellomedullary cistern alteration while a second opinion reported the same evidence as a cerebellar hypoplasia. Previous evaluations reported some tendency to laxity without any special classification or severity index. A posture with an anteposition of the shoulder was clearly visible. This was associated with an "obligatory" position of the shoulder blades and the spine. Lastly, the patient showed an evident tendency to the formation of inflammatory keloid, even when not related to particular skin wounds (Fig. 1).

The patient provide consent for the publication of her case.

Discussion

KBG syndrome was named after the initials of the last names of three original families reported in 1975. There have been over 100 patients reported in the literature, however the real prevalence is not known. It is an autosomal dominant disorder. This syndrome may be underdiagnosed because of the variable presentation and the features that can be mild and nonspecific. The clinical presentation of the patient fits with some of the major alteration described in literature. Among the most common are: macrodontia, anteverted nares, hypertelorism, triangular face, abnormal hair pattern, brachydactyly and clinodactyly, developmental delay, scoliosis, thick eye brow, vertebral fusion, cryptorchidism and short stature. However, a significant variability of the clinical findings has been reported even in the members of the same family (1, 2, 3, 4, 5, 6, 7, 8). From an orthopaedic point of view, skeletal anomalies have been reported in 75% of affected individuals (2, 8). Cervical ribs, posterior fusion defects, abnormal vertebral shapes, abnormal ribs, brachydactyly, clinodactyly, syndactyly of toes 2-3, kyphosis, scoliosis, hip dysplasia or Perthes disease, and sternum abnormalities are among the most common. A large anterior fontanelle with delayed closure, clavicular pseudoarthrosis and osteopenia have also been reported (2, 4, 5, 7, 8).

The patient referred a previous episode of stiffness to the left shoulder some years before and recurrent pain and stiffness to fingers and hands. This background, along with the clear clinical presentation of the right shoulder, guided the diagnosis. The range of motion (ROM) was severely restricted in both the active and passive mobilization, in rotations and flexion/extension. Exceeding the allowed ROM caused major pain. Years before, left shoulder symptoms were solved by some physiotherapy while in this occasion the patient referred an increased movement restriction and pain after few treatments. In our experience, steroid injections, hydrodistension, physiotherapy, and arthroscopic capsular release can be valid solutions for this pathology. However, hypertrophic scarring (keloid) can limit the results of a surgical procedure.

In a study by Low et al., one patient among the 32 evaluated, presented keloid scarring and another one hypermobile elbows (2). In 2019, Scarano et al. studying 12 unrelated patients showed that the majority of them (11 out of 12) presented joint stiffness. Therefore, the same authors suggested that this characteristic might be frequent but widely underestimated

(6). Ockeloen et al. has reported keloid formation in one patient among the 20 evaluated in their study (7). One of the two twins studied by Skjei et al. was affected by joint hypermobility (8).

An extensive literature on the adhesive capsulitis of the shoulder showed multiple risk factors. Almost all the papers on the subject report a correlation with autoimmune pathologies and endocrinological disorders, especially diabetes and those related to the thyroid. Additionally, it is far more common in women (9, 10, 11). Moreover, several studies have suggested that an immune response, which is at the beginning of this pathology, worsens the inflammatory synovitis that subsequently lead to capsular fibrosis (11, 12). Other studies on the physiopathology of the adhesive capsulitis reported the presence of B-lymphocytes, mast cells and macrophages as the immunological component of this pathology (13, 14).

The evaluation of shoulder with a limited ROM must include an accurate anamnesis if there is a suspect of adhesive capsulitis. Moreover, a tendency of keloid formation should always be taken into account when any kind of surgery is planned. This condition can be unusually negative for results especially in a tissue release surgery, thus the treatment of choice was non-surgical. In our common practice this pathology is treated with a steroid injection associated with mild hydrodistension and subsequent physiotherapy. However, if this treatment is not effective and/or the stiffness has been structured for a long time (6 months- 1 year) our choice is the circumferential release of the articular capsule in arthroscopy. In conclusion, one of the most recent studies on the subject (6) underlined the possible correlation between the KBG syndrome and joint stiffness (91.7%). Assuming that this association is not denied by new studies and that a possible correlation with an altered scarring is verified, a real association between adhesive capsulitis and this syndrome can be demonstrated. However, it is our common practice to be warned by the presence of syndromic alterations or autoimmune diseases (even if not completely diagnosed) in the suspicion of this shoulder pathology. Different alterations of the ANKRD11 (MIM611192) gene might not always fit in the exact same syndromic pattern and further studies, maybe comparing the few hypermobility cases, are needed.

Conclusion

We have presented a case of a young woman affected by KBG syndrome that suffered from adhesive capsulitis of the shoulders. This syndrome is likely to be more common than expected and it can often be unnoticed because of a nonspecific phenotype. We suggest that KBG syndrome might present a risk factor for adhesive capsulitis of the shoulder and joint stiffness in general. Moreover, the possible correlation with keloid formation would make this pathology even more challenging to treat. In addition, a patient with a similar phenotype, that has not carried out any evaluation, should be directed to a Geneticist.

Conflict of Interest: Each author declares that he or she has no commercial associations that might pose a conflict of interest in connection with the submitted article

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