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AGGRESSIVE FIBROMATOSIS, AETIOLOGY, DIAGNOSIS AND TREATMENT

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Summary

Aggressive fibromatosisrepresents (AF) a semimalignant tumour which has a locally destructive and invasive growth tendency but does not metastasize because of its high recurrence rate, the tumour remains a surgical problem. AF is rare group of fibroproletlative tumour started initially as painful masses developing slowly affecting mainly the limbs, neck, trunk, and the abdomen in that order. The disease process of (AF) regardless of the site of presentation, sex, or the age of the patient, endocrine, genetic and physical factors seem to play an important role in the development of the disease. Recent innovation in the field of molucular biology showed the abnormalities in (AF) is at the level of chromosomes in the form of gene mutation and chromosomal anomalies. Other studies showed that the pathogenesis of (AF) is related or modulates by hormone. Physical trauma seemed to have role in the development of the tumour. Whether (AF) is benign or malignant tumour is still in the field of theories. Many investigators put this type of tumour in the category of malignant lesion even in the absence of distal metastasis. The modalities of treatment of (AF) is widely different but surgery makes the major bulk, provided there is a good preoperative demonstration of the lesion by contrast solution and MR imaging, in the recurrent types of (AF) the combination of other modalities of treatment, radiotherapy, chemotherapy, cytotoxic and noncytotocix with and without surgery could be the most appropriate way of management. In this paper the character, pathogenesis, development method of detecting and the different modalities of treatment have been reviewed from literature.

Introduction

Aggressive fibromatosis is a group of fiberolefrative tumours of unknown etiology with strong behavious running between the benign and malignant tumours. Its presentation in different part of the body gives it different names and disease, it may present to general surgeon, orthopaedic, urologist and even dermatologist.

Most of its types are uncommon but its recurrent behaviour, controversy of its pathological reading and different modality of its management makes it an interesting tumour for the field of researches.

Aggressive fibromatosis are tumours arise from the fibrous tissue, from the fascia and desmoid tumour (from 'Desmos' = bound) are alternately used.

Usually they start initially as painful masses developing slowly and located in limbs 70% (girdle area); in the neck

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20%, the trunk 12% or the abdomen 2%[39].

Abdominal Aggressive fibromatosis are often associated with familial colic polyposis and it is then called gardner syndrome.

Aggressive fibromatosis show an unpredictable natural course with approximately 10% demonstrating a several aggressive growth pattern whereas others regress spontaneously.

Although generally the tumours are superficial, they are locally invasive, frequently involving adjacent neuro vascular stractures.

The disease process of Aggressive fibromatosis is the same regardless of the site of presentation, sex or the age of the patient.

The tumor grow slowly often recurs after excision does not metastize but has been reported to be fatal from local impingement of vital stracture (Ponser)[28]

Since it initial description by Stout, numerous article on aggressive fibromatoses have been published (Stout)[33].

The nomenclature of the type of tumors is very inconsistent. This lack of uniformity in termniology has lead to confusion. The armed forces institute of pathology recommends abandoning most of these terms and using the term aggressive fibromatoses (Lattes)[21]

Table 1

Aggressive fibromatosis
Congenital fibromatosis
Desmoid tumor
Desmoid fibromatosis
Differentiated fibromatosis
Diffuse muscular fibromatosis
Extra abdominal desmoid fibromatosis
fibrous hamartoma of infancy
generalized fibromatosis
Juvenile fibromatosis
Juvenile aponeurotic
Keloid fibromatosis
Myofibromatosis
Plantar fibromatosis

Terms used in literatures to describe fibroproliferative as locally recurrent lesions that do not metastasize.

AF tumors arise sporadically or as part of the extra intestinal manifestations of familial adenomatous polyposis (FAR). In (FAR) two distinct clinical presentation of the (AF) phenotype are seen:

1- One or few tumors present predominately in the abdominal wall or the abdomen.
2- A florid proliferation of tumors early in life mostly near the axial skeleton or extremities.

These different phenotype have been associated with different sites of germline mutation in the (APC) gene (Counture)[6].

Development of AF

The group of tumor of (AF) are benign soft tissue tumor arising from the connective tissue of muscle and overlying fascia or aponeuroses, the etiology behind it development is till unclear.

Endocrine, genetic and physical factors seem to play an important role in the development of the disease.

Protooncogenes are normal cellular genes that presumably regulate cell growth and differentiation, when these genes are altered by amputation, translocation or mutation the MRNA and protein encoded by the gene may be expressed abnormally.

One such protooncogene which has the potential to play a role in fibroprolifrative lesions, is C-sis. The gene for C-sis is located on chromosome 22 and encoded for the B-chain of the platelet derived growth factor PDGF (Antoniades MN)[29].

Like chains can also combine to form an active homodimeric protein. B chain combine to form PDGF-2.

Normal fibrocytes do not express C-sis but have receptors. For PDGF population of cells in the tumour mass expresses C-sis and produce PDGF2 a

mechanism for the pathogenesis of (AF) is suggested.

The trigger for this increase expression is not known but could be related to or modulated by the sex steroid hormones and receptors. The expression of C-sis lead to increased PDGF-2 in the extracellular space surrounding the cell.

The PDGF-2 acts as a mitogen on surrounding fibrocytes and on the cells that express C-sis[36].

Seventy five percent of cases harbor asomatic mutation in either the APC or beta-catenin genes, resulting in beta-catenin protein stabilization. Cyclo-oxygenase-2 (Cox-2).

(Cox-2) is an enzyme involved in prostaglandin synthesis that modulates the formation of colonic neoplasia, especially in cases due to mutations resulting in B-catenin stabilization. Human (AF) demonstrated elevated (Cox-2) levels[27].

The mitogenic effect on the cells expressing C-sis causes a type of autocrine and paracrine loop in which the abdominal cell stimulates itself to make more products, reproduce and produce more PDGF[2].

PDFG has a short half life and would be unlikely to be more into the systemic circulation in measurable or active concentration (Bowen)[4].

An association has been reported between trauma and (AF), the report of development of (DT) around the hip 45 months after implantation of total hip prosthesis is a good example. Although soft tissue tumour induced by metalic implants have been observed clinically there is a search for a coherent explanation for the exact pathogenes (Gebhart)[13].

DT developing around silicon implant have also been published in the world literature.

A case report of young 12-year old male patient who developed a fusiform mass on the volar aspect of his left forearm following two fractures. Microscopic feature reveal a juxcortical (AF)[8].

In most of the cases the pathobiology of (AF) is detected at the level of genes resulting in the identification of abnormalities in both DNA and RNA content of human tissue.

Recent innovation in the field of molecular biology have made the techniques for identification of abnormalities in both DNA and RNA content of human tissues more readily available.

Northern blot analysis identifies mRNA expression in biologic tissue, in situ hybridization, localizes the site of mRNA expression, and immuno fluorescence examines the in vitro production of growth factors and receptors (Benjamin)[5].

The abnormalities of the cell biology in (AF) is in the form of gene mutation and chromosomal anomalies.

Sixteen cases of (DT) were studied by immunohistochemistry for counting stromal blood vessels and proliferative activity, DNA flow cytometry and interphase cytogenetic analysis of chromosome 8 by flurescence in-situ hybridization (FISH). In flow cytometric analysis, all the cases examined showed a diploid pattern.

The (FISH) study revealed that the incidence of trisomy 8 was significantly higher in the recurrent DT (72.7%) (Kouho)[19] while in the non-recurrent cases (12.5%).

DT arise sporadically or as part of the extraintestinal manifestation of familial adenomatous polyposis (FAP).

These different phenotype have been associated with different site of germline mutations in the (APC) gene. Immunihistochemistry on the tumour also demonstrated elevated level of Beta-catenin[6].

A non-random occurrence of trisomy 8 and of trisomy 20 in (DT) has been recently reported.

A nonrandom occurrence of trisomy 8 and of trisomy 20 in desmoid tumour has been recently reported. The finding of trisomy 8 in non-dividing desmiod

tumour cells by in situ hybrization prompted us to evaluate, in similar way, the occurrence of trisomy 20 and cyto- 1) genetically observed in few cases.

Double flurescence in situ hybridization (FISH) with centromeric probes for chromosomes 8 and 20 was performed on 16 single cell suspensions of (DT). FICS confirmed the occurrence on 16 single cell suspensions of DT.

FISH confirmed the occurrence of trisomy 5 or 20 in a single cell suspension of DT.

Both individual trisomies and even more their association in the same cells are rare to extremely rare in solid tumours in general and in mesenchymal tumours in particular and are only known to occur in infantile fibrosarcoma (Qi)[30].

The chromosome abnormality may play a role in the occurrence of (AF). A 2) report of case with muscular dystrophy develop an extraabdominal DT showing abberrant chromosome. Cytogenetic analysis of the tumour showed a clonal karyotypic abnormality (Katsuura)[17].

Beta catenin nuclear expression correlated with cyclin D1 overexpression in sporadic (DT) which could be an in vivo model system for the APC-beta-catenin-TCF pathway. In addition, beta catenin mutations in DT occurred at an unusually wide range of sites within the gene (Tanaka)[37].

Pathology

The musculoskeletal fibromotosis comprise a wide range of lesions with a common histopathological appearance. The main pathology consist of proliferating fibroblast, uniformally elongated cells separated by variable amounts of collagen. The histological appearance is similar to normal fascia except that cells were somewhat plumper and of greater density. Most of the patients initially had an asymtomatic mass without functional loss.

They can be divided into two major groups (Ovesen)[25]:

Superficial group: They are typically small, slow growing lesions and include palmer and planter fibroma-tosis, juvenile aponeurotic fibroma and infantile digital fibroma.

Those of the palm are often associated with Dupnytern's contructure. The lesion may start as a painless, subcutaneos nodule, the contracture developing later as other nodules appear, eventually, the entire fascia may become thickened.

Microscopically both palmer and platnar fibromatosis are proliferative fibroblastic lesions usually seen as nodules that blend gradually with the surrounding fascia. Mitoses may be present but ordinarily no abundant. Collagenation eventually occurs.

The deep fibromatosis groups are commonly large may grow rapidly and more aggressive, they include infantile myofibromatosis, infantile aggressive fibromatosis, fibromatosis coli and extraabdominal dismoid tumour. They are highly collagenized and rather sparselly cellular and infiltrate the muscle in which they develop.

Grossly they are dense, hard, rubbery and grayish white. Those of the shoulder gridle usually run a benign course, whereas those of the pelvic girdle are somewhat more aggressive (Garnesale)[11].

The margin of the tumour with high cellular materil and less collagen are called tumours with positive margin whereas those tumours with high collagenized tissue are called tumour with negative margin.

These two classifications are important criteria for the dignosis, treatment and rate of recurrence of the tumour. Margin status is the most important predictor of local recurrence for patients with resectable unifocal (DT) (Goy)[12].

Radiologic finding

Conventional radiologic procedures are poor at demonstrating the extent and the type of tumour.

Modern tomographic methods are more able to determine the size of the lesion and combination of angiography and CT can frequently provide definite diagnosis (Weismann)[40].

The superior contrast resolution of MR imaging, its capability of demonstrating lesions not clearly identified by CT, its pluridirectional capabilities and its ability to demonstrate large soft tissue tumour in a single coronal or sagittal plane makes it the preferral initial modality for evaluation of soft tissue tumour of uncertain aetiology and also in the follow up of these patients (Sundoram)[34].

In MRI the tumour signal intensity ranged from being low to isointense with respect to muscle on T1 weighted images while being predominantly of hetrogenous increased signal intensity on T2-weighted image. The post contrast study demonstrate diffuse tumour enhancement (O'Keefe)[24].

Imaging is important as with other neoplasms in delineating the extant of involvement for staging purposes.

The triple bone scintigraphy demonstrated increase flow and radiotracer pooling in the areas of tumours on dynamic flow and immediate blood pool images, respectively this additional information can be particularly useful in patients with equivocal or questionable histologic diagnosis especially from small unrepresentative biopsy (Thakroe)[38].

Associated condition

1) Congenital bowing of the ulna and (AF).

   The association of skeletal anomalies and (AF) has been documented. Isolated bowing of the ulna is rare, yet it occurrence, particularly in conjunction with congenital dislocation of the radial head has been documented (Eady)[9].

2) Melorheostosis is associated with DT (Ippolitov)[16]

3) Desmiod tumours arise sporadically or as part of the intraintestinal manifestations of familial adeno-matous polyposis and it is then called gardner syndrome.

4) Muscular dystrophy[17].

5) Dupuytern's contracture.

Fibroma and fibrosarcoma?

Although the etiology of (AF) is still in the field of theories, the behaviour of its recurrence leads many investigator to put this type of tumour in the category of malignant lesion even in the absence of distal metastases. The study of the biochemical changes in (AF) give an important evidence of its malignant behaviour.

There is a hypothesis that the exuberant fibrosis (AF) may result from the initiation of molecular events producing increased expression of cytokines. The result of this study showed localized increased expression of cytokines epidermal growth factor, transforming growth factor-beta, tumour necrosis factor-alpha, vascular endothelial growth factor, interleukin-1 beta and interleukin-6 in the endoltelial cells of blood vessels in the tumour. The conclusion was that the increased expression of cytokines associated with angiogenesis usually found in wound healing and invasive tumours may contribute to the pathophysioogy of (AF) (Mill)[23].

Although an overlap exist between (AF) and benign group, high values of pyrnvate kinase (PK) activity are indicative of grade 2 and 3 malignancy. Significant shifts in isozyme pattern favouring the expression of k-type subunits where found in tumour with pattern of PK in (AF) may act as another

argument to place them in the category of malignant fibroblastic tumours (Eibers)[10].

AF is caused by germline mutation in the (APC) gene. APC is involved in the regualtion of the beta-catenin which is a mediator cellular level in wansingnaling. Immunohistochemistry showed an elevated beta-catenin protein level in all tumours regardless of mutational status.

The demonstration of mutations in two mediators in the wnt-Apc-betacatenin pathway implicates beta-catenin stabilization as the key factor in the pathogenesis of (AF) (Tejpar)[36].

The protoencogens C-fos has been implicated in the development of both benign and malignant lesions of bone. They found detectable level of C-FOS expression in tissue from the extra abdominal fibromatosis, firbo dysplasia, fibrosarcoma and malignant fibroushistiocytoma of bone. All fibrous lesions consistently demonstrated high level of expression in majority of cells in each lesion.

Chondrosarcomas and osteosarcomas exhibited more heterogeneity in C-FOS expression than fibrous tissues.

These indicate that the expression of C-FOS may be important in the development of a broad range of fibrous lesions as well as in bone and cartilaginous tumours (Weisstein)[41].

Whether fibromatosis are neoplastic reactive lesions or not is a site of controversial and the relationship, if any, between the superficial and deep forms are poorly understood. Clinical, pathological and cytogenetic data of 78 cases of fibromatosis were analysed and correlated with each other. The results demonstrate that clonal chromosome aberrations are a common features of this entity, being present in 46% of DT, although less frequent in the superficial types (10%)[17].

In the deep-seated extra-abdominal fibromatosis, trisomies 8 and 20 and loss of 59 material were the only recurrent features.

No correlation between trisomies 8 and local recurrence was found.

De-Wever[7] findings provide additional evidence for the neoplastic nature of fibromatosis.

Management of AF consist of:

Surgery
Hormonal therapy
Non cytotoxic therapy
Cytotoxic therapy
Radiotherapy
Combination of the above modalities

I-Surgery:

Surgery is the main treatment for (AF) but it is not curative because of the infiltrative nature and tendency to recur. Determing the anatomic extent of the tumour is a major factor in planning operative intervention.

Among many treatments recommended in the past, wide excision has been successful even in difficult cases.

Margin status of the tumour is the most important predictor of local recurrence for patients with respectable, unifocal DT (Goy)[12].

Wide margin excision may only be regarded as an option if safety margin of at least 2 cm is guaranteed. Even under these circumstances recurrence rate are very high. Debulking operation invariably lead to a boost towards more aggressive growth (Peterschulte)[29].

If the disease affecting 4 or more muscles we recommend wide local excision in all anatomic area that allow this procedure.

When major nerve and vessels are involved we recommend intra-lesional exicion with wide margins in order to preserve limb function (Higakis S).

Amputation should be reserved for cases in which the disease or its treatment have resulted in a non-

functional or chronically painful extremity (Spiegel)[32].

II.Hormonal therapy

The review of the literature reveals that the biology of this disease is related to the endogenous hormonal environment and that estrogen and progesterone receptors have been documented. Tomoxifen has been maintained over several years of treatment lead to tumour regression. In other patient with inoperable mesenteric fibromatosis, the tumour progressed on tamoxifen but regressed after treatment with xoladex (gaserelin ocetate) and medroxy progesterone acetate[26]. The author recommend that endocrine treatment be employed in inoperable DT or when there has been post surgical recurrence (Wilcken)[42].

III.Non-cytotoxic drugs

AF is a locally invasive soft tissue lesion, 75% of cases harbor somatic mutation in either the APC or beta-catenin genes resulting in betacatenin protien stabilization.

Cyclooxygenase-2 (cox-2) is an enzyme involved in prostaglandin synthesis that modulate the formation of colonic neoplasia especially in cases due to mutation resulting in beta-catenin stabilization. (Cox-2) partially regulates proliferation due to betacatenin stabilization in (AF). Although cox-2 blockade alone does not cause tumour regression. This data suggests that it may have a role as an adjuvant therapy to slow tumour growth in this lesion (Poon)[27].

Antiestrogen and nonsteroidal anti-inflammatory drugs have been shown to be effective in adult patients with unresectable or recurrence (AF) tumour.

1- The antiestrogen treatment may inhibit further proliferation of tumour cells.

2- Non-steroidal drugs are thought to be effective through their interference with prostaglandin metabolism (Lackner)[20].

3- Retrospective analysis was undertaken to evaluate the toxicity and efficacy of treatment with interferon-alpha +/- tretion. The data of this retrospective-nonrandomized study on therapy suggest that such treatment may be effective in prolonging the disease-free interval of patient after intralesional or marginal surgery (Leithner)[22].

Surgery for (AF) in shoulder would probably have a permanent impair muscle function therefore, interferon. Alpha treatment (0.9 million I.U. twice daily subcutaneously) was given. This treatment modality may be considered as an alternative to mutilating surgery in patient with (AF) (Hardell)[14].

IV.Radiotherapy

Radiotherapy is an adjuvant therapy in treating resectable (AF). Margin status is the most important predictor for local recurrence for patients with positive margins following wide exci-sion of recurrent disease.

Adjuvant radiotherapy is less likely to benefit those with clear margins due to excellent results for these patient treated with surgery alone.

The local control of (AF) in the adjuvant setting is excellent with total doses ranging from 50-60 Gy, with acceptable morbidity (Gay)[12].

Radiation should be used as a last resort in skletally immature because of the risk of growth disturbance, contracture and secondly malignancy.

Radiotherapy can contribute to improve prognosis for (AF) under the following circumstances:

When the tumour cannot be resected with histologically clear margins or when resection margins are question-able.

When the patient is 30 years old or above.

When the tumour is inoperable or resectable only by means of mutilating operations (Wallter)[39].

V-Chemotherapy

Chemotherapy may have role in children with inoperable disease, in those who have gross residual tumour after intralesional procedure, for disease progression or recurrence. Neoadjuvant therapy should be investigated as a means to achieve wide margin in some cases (Spiegal)[32].

Methotexate plus vinblastine given every 7-10 days for several months is associated with prolonged stable disease in substantial subset of patients with advanced (inoperable) AF (Azzarelli)[3].

In situation of local recurrence despite previous wide local excision a trial of a-multiple-agent chemotherapy incorpora-ting vincristine, actinomycin-D and cyclophosphamide may be indicated in b-an attempt to control the disease (Raney)[13].

Three patients with (AF) showed a c-complete remission after regional isolation perfusion with cytotoxic. The cytotoxic used were doxorubicin, d-melphalon and combination of these agents.

This treatment regemen in form of toxicity and tissue necrosis can be controlled by adjustment of the dosage and dose distribution of doxorubicin but the morbidity after perfusion with doxoribicin remained considerable (Klaase)[18].

Conclusion

1) Aggressive fibromatosis is the term that should be used to avoid confusion with others very in consistent terminology.
2) Chromosomes abnormality may play a role in the occurrence of (AF). The study of the tumour at the level of cell pathology is important tool for the diagnosis. Northern bolt analysis and flourscent in situ hybridization (FISH) are important techniques for identification of abnormalities in both DNA and RNA content of human tissue.
3) Some of the biochemical factors may be initiated or produced by the tum-our. The detection of these factors may help in the diagnosis or treatment of (AF), the followings are examples:

Human (AF) demonstrate eleva-ted cyclooxygenase-2 level.

Population of cells in the tumour mass express C-sis and produces PDGF-2.

Immunohistochemistry study of the tumour demonstrates elevated level of Beta-catenin.

Aggressive fibromatosis may result from the initiation of mole-cular events producing increased expression of cytokines.

4) The recommended treatment remains controversial.
5) One way out of this dilemma is the establishment of clinical classifica-tion as a first step toward standard-ized therapy.
6) Although surgery is the first option in the treatment of (AF), it appears to have a triggering effect on the growth of the tumour.
7) MR imaging is important toll for preoperative planning for surgery.

Tumour with positive margins are mostly sensitive to radiotherapy.

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