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Review on Stoneman Syndrome: A Rare Genetic Disease

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ABSTRACT: Stoneman syndrome or FibrodysplasiaOssificansProgressiva (FOP) or Munchmeyer's disease is an unprecedented genetic sickness of disabling connective tissue and ectopic tender tissue calcification with hand and foot deformities, leading to severe limitations of joint movement. This condition occurs by the mutation in the bone morphogenetic protein (BMP) type 1 (Activin-A Receptor- ACVR1) which leads to dysregulated bone formation. People with FOP usually have a median life expectancy of 40 years. Most of the patients are Wheelchair-bound by the end of the alternate decade of their life and normally die because of complications of thoracic insufficiency syndrome. There's no cure or treatment present till this time, however implicit treatment based on future interventions may inhibit the ACVR1 gene. Currently, treatment options available for FOP are restrained and emphasizing the need for innovative therapeutic processes. Challenges to increase the management criteria for FOP consist of several problems in recruitment due to the rarity of FOP, disease variability, the absence of reliable biomarkers, and moral issues regarding placebo-controlled trials. This narrative review provides an overview of the disease and explores arising strategies for FOP treatment.

KEYWORDS: Stoneman syndrome, FibrodysplasiaOssificansProgressiva, Mutation, Bone morphogenic protein, Activin- A Receptor (ACVR1 or ALK2).

I. INTRODUCTION

Stoneman Syndrome is defined as a rare genetic disorder, where tissues like tendons and ligaments show the abnormal growth of the bones outside the skeleton system. The muscle tissue and connective tissue get ossified (also known as heterotopic bone) which restricts the movement of the bones and affects an individual's life. Since the disease is genetic, the growth of extra bones can be seen in early childhood itself, beginning from the neck and proceeding downwards in the body into the limbs. Patients suffering from FOP generally have big malformed toes [1].

This is a very different symptom when compared with other skeleton parts and muscle associated disorder, which showcase a big malformed toes alongside shorter thumbs, skeletal abnormalities and growths. Extra-skeletal inside the neck area may cause difficulty in neck and mouth movement. It makes it more difficult for the patient to communicate, eat and rotate their neck freely. The growth of heterotopic bone does not prevent on its own, leading to more severe problems in the later section of existence, the bone that once influences the neck and mouth region will typically make its way downwards within the body from shoulders to backbone and similarly to limbs. This may put stress on other physical organs like lungs and rib cage making it hard for the patient to breathe. [2]

The unusual growth may make an individual's overall body fragile and risk an external threat to the body. Any physical trauma to the muscle like a fall or invasive medical approaches can cause myositis (muscle swelling and inflammation) and may boost the process of ossification in the affected area. In females, the HO (heterotopic bone) in lower back and limbs can make it difficult to conceive and may retain the growth of the foetus during pregnancy. It is advised by the medical experts not to conceive, if treatment is going on. However, during pregnancy it is better to keep away from any stress on the body.

II. HISTORY OF STONE MAN SYNDROME

Stone man syndrome or FOP was first pronounced in the scientific literature in the 17th century. FOP was referred as bone myositis at that time and it was thought that muscle inflammation causes outgrowth of bone formation in patients.

In 1671, The French physician Dr. Guy Patin was the first who describe the stoneman Syndrome and later in 1692, he detected the patient with FOP who becomes stone or wood (Fig. 1).

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Fig.1: Physician Dr. Guy Patin

In 1970, the ailment was renamed by Victor A. Mckusick who stated the disorder influences Apart from muscles mass (e.g., Ligament, tendons). In April 2006, an international team of Exploration Ers led by Dr. Eileen M. Shore, a cell and molecular biologist, and Dr. Frederick S. Kaplan, a research fellow at the University of Pennsyl-Vania, published the results of their FOP Exploration that revealed the mutation.

The best known case of FOP is of Harry Eastlack (1933-1973). His circumstances started out at the age of ten and by the time of his death from pneumonia in November 1973, His body had completely ossified leaving him capable to move only his lips. He never met any other person with FOP during his continuance. Harry Eastlack bestowed his body to Science and his skeleton is now at the Mutter Museum in Philadelphia to study the FOP(Fig. 2). [5]

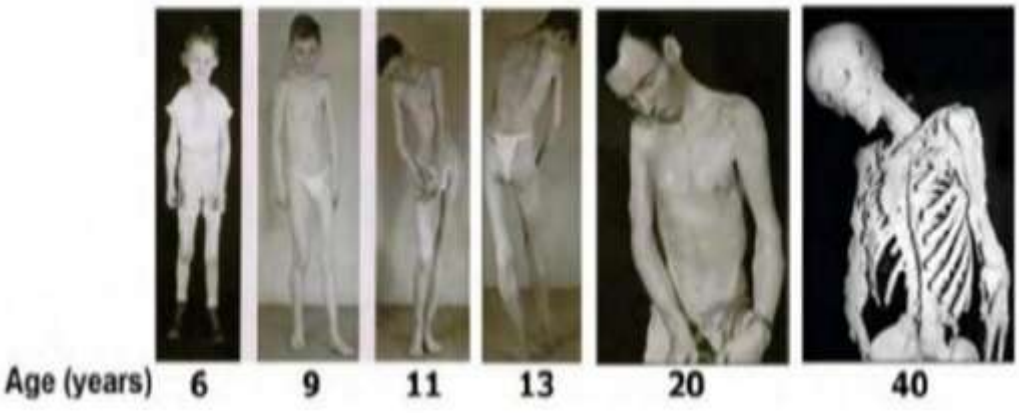

Fig. 2: Images of Mr. Harry Eastlack with Stoneman Syndrome, who began his symptoms at the age of 10 and died at the age of 40

III. MUTATION OF FOP

FOP Is a monogenic circumstances which usually associated with mutation in the ACVR1 or ALK2 Gene present on chromosome 2, which perform a major role in signalling of BMP receptors.

IV. BMP RECEPTORS

Bone morphogenetic protein receptors is part of serine- threonine kinase receptors. It comes under the TGF – Beta super family receptors. It is classified into four types which are BMP type1, BMP type 2, ACVR1, BMPR1A/BMPR1B. ACVR1 is a sort of BMP Receptor which encoded Via ACVR1 gene. In 2006, It was recognized that Arg206His (R206H) ACVR1 gene mutation was responsible for FOP. R206H mutation causes ligand independent BMP signalling and Increases BMP responsiveness by growing SMAD1/5/8 signalling. [13]

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V. GENERAL MECHANISM

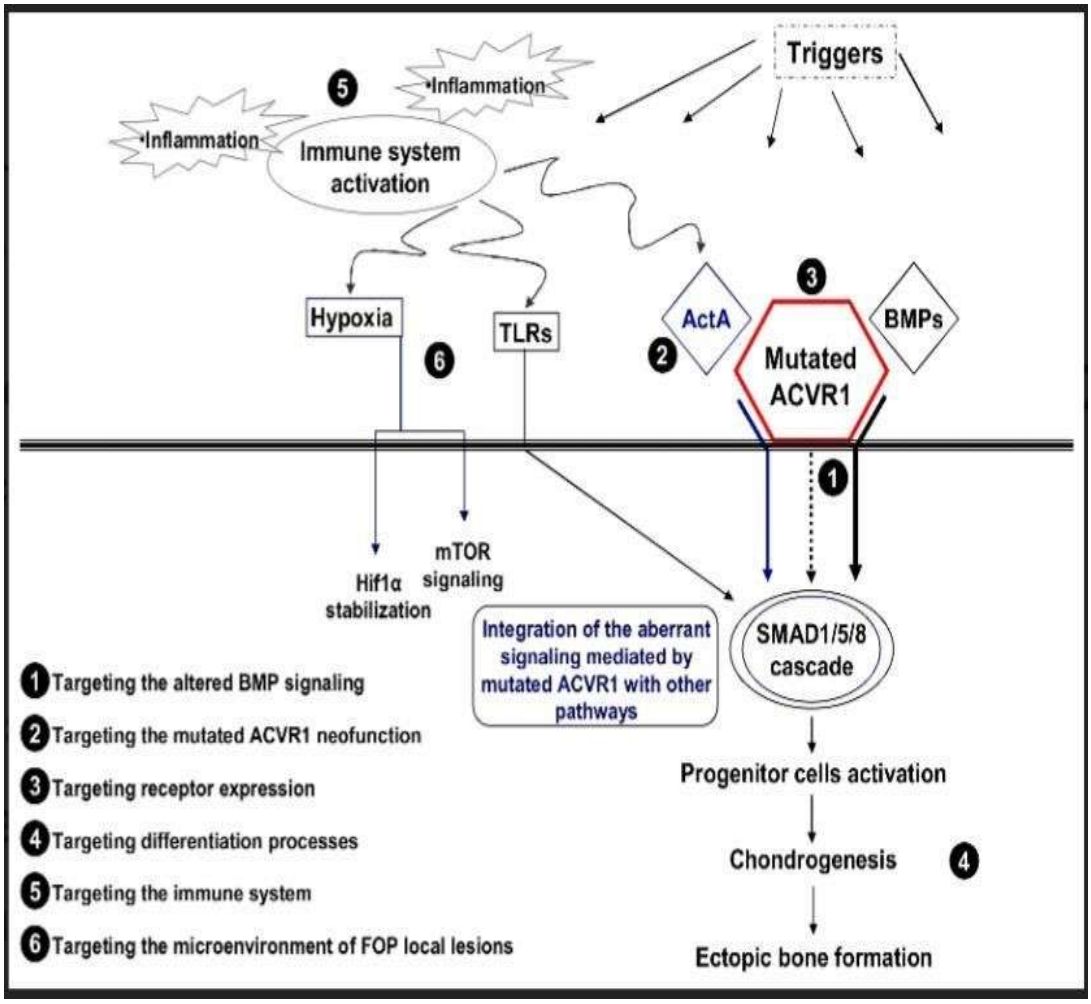

Fig. 3: Schematic representation of molecular and cellular events

VI.ACVR1 SIGNALLING AND TRANSCRIPTION

When numerous growth factors acts as ligand for BMP receptors which binds to ACVR1 Receptors, intracellular signalling is regulated by means of regulatory molecules referred as Receptor regulated SMAD (R -SMAD), these are transcriptional factors that change over the greater ligand signalling from cell membrane bound ACVR1 Receptors into nucleus, where they generate the transcription of ACVR1 target genes.[17] There are various SMAD molecules which might been signalised by means of specific signalling molecules are SMAD1/2/3/5/8. These are R-SMAD's and SMAD4 also called as common companion SMAD (Co-SMAD), which carrying out intracellular signalling while R-SMAD's are activated. I-SMAD's also called as Inhibitory SMAD's (SMAD6/7) compete with SMAD4 and affect the Modulation of ACVR1 regulated transcription.

TGF-β superfamily receptors have two monomeric receptor Subunits, TGFβ type 1 monomer and TGFβ Type 2 monomer. Type 2 monomers have extracellular cysteine rich domains for binding of ligands, on binding of ligands to kind 2 receptor causes dimerization of Type 2 Receptors, It Signalises recruitment of type1 receptors, due to kinase Activity of Type 2 Receptors phosphorylates serine residues of intracellular area of Type 1 receptors forming a Heterotetrameric complex, recruits R-SMAD's, bind to Terameric complexes at L-45 region of Type1 receptor.

Recruitment of R-SMAD is facilitated by unique proteins Called SARA, which anchors cell Membrane and facilitates RSMAD's to bind to type 1 receptors. Due the kinase action of type1

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Receptors phosphorylates R-SMAD's, causing Conformational alternate at their MH2 domain (activated RSMAD). Activated R-SMAD's alerts the binding of Co-SMAD, Forms R-SMAD, and CoSMAD Complex that transcribes the Genes that regulates osteogenesis, neurogenesis and Ventral mesoderm specification. [19] [fig.4]

Activin-A is a ligand for TGFβ receptors, these receptors mediate intracellular signalling via SMAD2/3, but in R206H Mutation activin -A stimulates SMAD1/5/8, enhances Endochondral ossification and chondrogenesis (i.e., ligand Independent BMP signalling).Resulting in secondary Skeleton formation (heterotopic ossification) in the gentle tissues limiting the mobility.

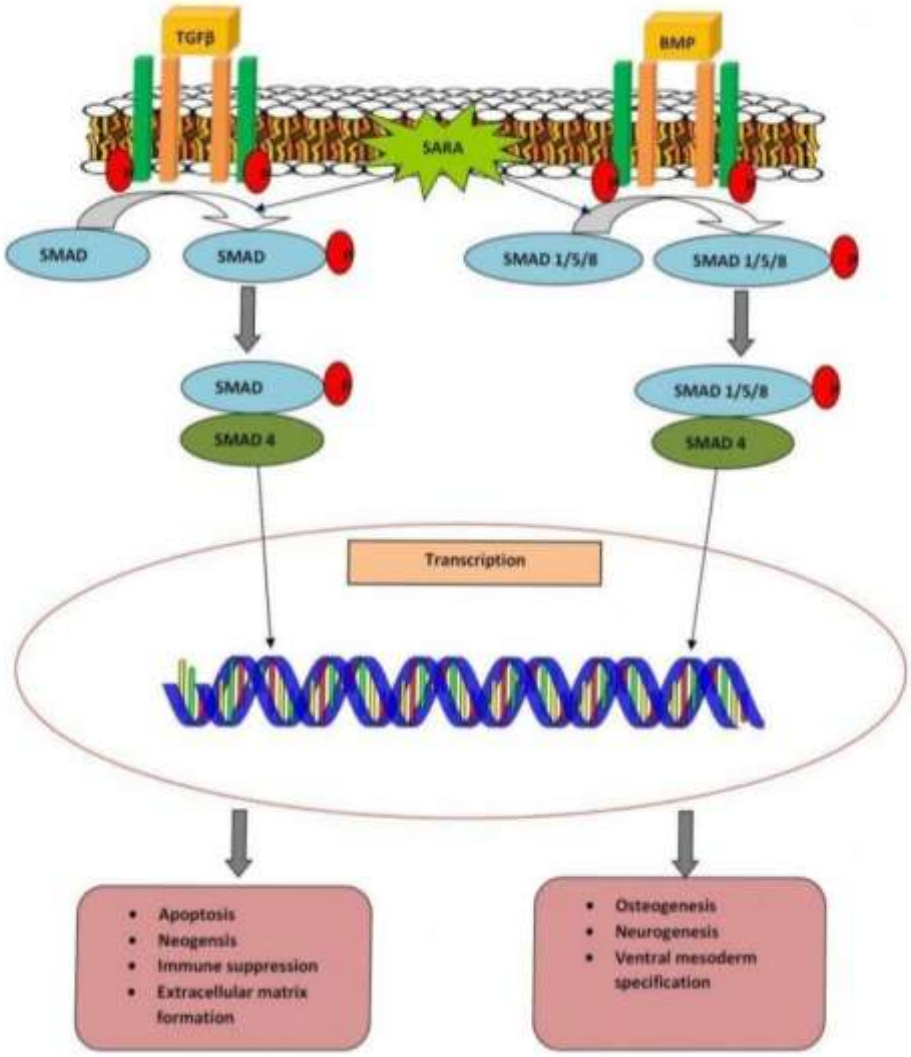

Fig. 4: Pathway signalling of FOP

VII. CAUSES OF FOP

Fibrodysplasia Ossificans Progressiva is a serious condition that leads to a discomfort and difficulty in further body movement. A mutation of the ACVR1 gene causes Stoneman Syndrome condition. ACVR1 gene is found in many tissues of the body which includes cartilage and skeletal muscle is answerable for the mapping of bone morphogenetic protein (BMP) kind I receptors. BMP controls how the bones and muscles grow and develop.

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However, maximum cases arise sporadically as a result of new ACVR1 mutation. This genetic mutation causes substitution of codon 206 from arginine to histidine in the ACVR1 protein, resulting in irregular activation of ACVR1, leading to the metamorphosis of Connective and Muscle tissue into a secondary Skeleton [19], responsible for controlling the development of the muscles and bones, including the gradational relief of cartilage by bone (ossification) that occurs in ordinary skeletal maturation from birth to young adulthood. This causes Endothelial cells to transfigure to mesenchymal stem cells and also to bone.

It is far an autosomal dominant situation, which means simplest one biological parent need, to skip the altered gene to the child for them to inherit it. If determine has the gene that causes Fibrodysplasia Ossificans Progressiva, there's a 50% chance that the child will inherit the condition.

Some of causes are:

1) Gene mutation (ACVR1 gene) present at beginning (birth).
2) Chemical defect in particular one protein.
3) Presence if an abnormal bone tissue at single site in a bone.
4) Cardiorespiratory failure from thoracic insufficiency syndrome (death in some cases).

The great news is that, the cases of Fibrodysplasia Ossificans are very less, the possibility of the case is 1 in 2 million people globally.

VIII. SYMPTOMS

The nature of the genetic sickness makes it both easy and tough to determine. Since, FOP is quite rare and lesser known by the general people, one may confuse it with extremely different muscular disorders. Marked symptoms of this disorder make it easy to diagnose. This process generally becomes noticeable in early childhood; the bone growth generally progresses from the top of the body downward.

A symptom of the situation that leads to an FOP analysis is a malformed and short big toe FOP results in cervical spine abnormalities which appear as massive posterior elements, tall restricted vertebral bodies, and fusion of the hand joints between C2 and C7. [24] The cervical spine often become ankylosed early in life (Fig. 5).

that Every so often grows inward and over the second toe. Growth variations of the big toes are Visible at birth, even before other symptoms appear fig. 5 [20]. Almost 50% of cases of FOP additionally have malformations of the thumbs just like the big toe.

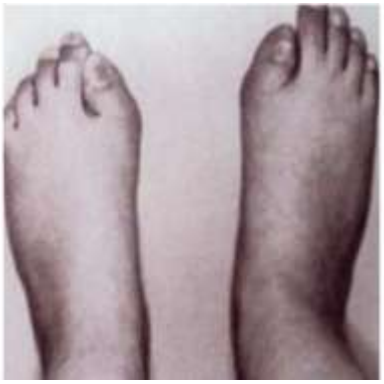

Fig. 5: Malformation of toes at birth

The primary symptom of Fibrodysplasia Ossificans Progressiva is the slow replacement of Muscles tissue, tendons and ligaments into bone (heterotopic ossification). This method starts at the neck and shoulders in early childhood or at the time of birth and development throughout the body over time. The development of bone may be fast in some cases, or very slow in others. Each case is unique.

Abnormal bone development occur spontaneously which begins with soft tissue damage Caused by viral diseases. It is commonly seen in tendon, ligaments, skeletal muscle tissue and Connective tissue (fascia and muscle fibres).

Symptoms begin during flare-ups, which are your body's reaction to trauma that could be from an injury, surgical procedure or viral infection like the flu. Swelling can cause increase in size and newly formed part of the frame, can be painful. When flare-ups occur, the bone Morphogenic protein kind Type 1 Receptors fail to prevent producing proteins, which causes new Bone to shape on muscles, tendons and ligaments. After new bone forms, swelling decreases, which can take everywhere from a few days to a month.

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Fig. 6: Cervical spine ankylosed

Symptoms of Fibrodysplasia Ossificans Progressiva include:

1) Bone forming on muscles, ligaments and connective tissue.
2) Difficulty in respiration, eating and speaking.
3) Hearing impairment.
4) Swelling of soft tissues and deformed spine.
5) Decreased mobility (scooting instead of crawling, joint stiffness, locked joints).
6) Malformed big toe and Permanent immobility.
7) Red to purple, painful and hot to the touch areas of the body that look like tumours.
8) Frequent imbalance while moving followed by low-grade fever, inflammation, and joint pain.
9) Surface reflection of abnormal bone growth throughout the body (except the Tongue, Diaphragm, extra ocular muscles mass, cardiac muscle, and smooth muscle).

The Human Phenotype Ontology (HPO)-European Rare disease database (from orphanet) shows that in approximately 80-99% of cases. The most generally observed symptoms of all others are Abnormality of the first metatarsal bone, cervical abnormalities, Ectopic Ossification in ligament tissue and muscle tissue, hindrance of joint mobility, short hallux, Spinal rigidity, subcutaneous nodules and alopecia [13].

IX. DIAGNOSIS

Stoneman syndrome is so rare disorder that diagnosis is very difficult which sometimes Misdiagnosed with more common disease such as cancer or fibrosis. Only difference that helps to identify this disease from other skeletal problems is malformed toes and thumbs.

Diagnosis is mainly based on radiographic imaging findings, magnetic resonance imaging, plain X– rays, conventional radiography and confirmatory genetic testing techniques to identify this disease. The disease clinically identified by elevated levels of alkaline Phosphatase and bone specific alkaline phosphatase. [28]

Genetic testing registry (GTR) and Imaging tests will help to choose appropriate genetic testing and overall growth of the heterotrophic bone. GTR is conducted by a group of medical Professionals that majorly deals with research and analysis of such rare conditions. It consist a series of Questions for both patient and the medical team. The Most definitive test to confirm the analysis of stone man syndrome is molecular genetic testing for the ACVR1 Gene to determine whether or not there is a mutation.

Characteristic imaging and clinical findings:

- Bilateral hallux valgus deformity
- Monophalangic (great toes).
- C2-C7 facet joint fusion.
- Short first metacarpal/metatarsals
- Heterotopic ossification of muscles and connective Tissues.
- Tall narrow vertebral bodies
- Large posterior elements.

Other techniques which are help to identify this disease are Differential diagnosis, Genetic Counselling, Antenatal testing and Management including diagnosis (flare– ups).

X. TREATMENT

Genetic disorders like stoneman syndrome do not have an effective treatment or preventive to cure the disease. It only helps to suppress or relief the pain. Currently FOP is controlled by supportive therapy which is based on the early prognosis of the condition and avoiding injuries, and providing symptomatic Relief in cases of painful flare-ups by conservative use of Analgesics, corticosteroids, Anti– inflammatory drugs and preserving residual functions, with last Option of surgery.

Surgical excision is considered when there is excessive pain, joint limitation, or nerve compression is present. Surgical procedure is normally cautioned when myositis ossificans is ripe, identified by a better bone density in x-ray findings and normal Erythrocyte Sedimentation rate and alkaline Phosphatase level. [27]

Medical professionals have come up with some medications that slow down the increment and intensity of Ossification:

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1. High dosage of corticosteroids like Prednisone to reduce pain and swelling flare-up which Seen in the early stages. It is considered as first line treatment. It is recommended to be taken within 24hrs as the first line Flare-up (4 day course of high dose), before non-steroidal anti-inflammatory drugs (NSAIDs) or medicines which need to be given between flare-ups.
2. Muscle relaxants and Mast cell inhibitors.
3. Amino bisphosphonates.
4. Occupational therapy.
5. Assistive devices such as braces or special shoes to help with walking.

In children, restriction of physically interactive play may be Helpful to reduce falls. Improvement in household protection, Use of ambulatory devices, protective headgear and modification in their activities are some of the strategies to Prevent falls and minimize the risk of injury when children Fall. Physical rehabilitation improves the daily living activities by approaches that avoid passive range of motion which could lead to disease flare-ups. Occupational therapy and vocational education consultations may be useful approach. [11]

In recent, the novel therapeutic treatment or approaches for this disease have been developing. It includes Gene therapy which targets CRISPR – Cas9, RNA interference and Adeno – associated virus vectors receptors for treating FOP. Receptor targeting, Stem cells, Immunotherapy and Nanoparticle delivery system techniques are useful to cure and treating Stoneman Syndrome. [4]

XI. CONCLUSION

Stoneman syndrome is a rare genetic disorder of connective tissue. It is misdiagnosed due to common presentation of acquired or congenital disease which may results early disability, paralysis and inappropriate surgical treatment. Most of the patients with FOP are bedridden by an early age of 20 and the lifespan can be extended to 40 yr. There is no cure to this condition. But by the use of some effective treatment and techniques. We can easily diagnosed this disease and overcome the problems. We need to spread the Knowledge to physicians, patients, family members and other people about the disease, as well as its features for early opinion and how to prevent flare-up of the disease to promote better quality of life in these cases.

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