INPLASY

Clinical characteristics, therapeutic options and outcomes in hyperphosphatemic tumoral calcinosis: a systematic review

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 December 2023 and was last updated on 18 December 2023.

INTRODUCTION

Review question / Objective Hyperphosphatemic tumoral calcinosis (HTC) is a clinical condition characterized by periarticular chunky calcification, inflammatory joint pain and restricted mobility. Treatment options include phosphate lowering therapies and symptomatic measures. Responses to treatment reported in literature are variable. A systematic review was performed to better understand the myriad presentation, various therapeutic options, response to therapy and its clinical implications.

Rationale Given the rarity of tumoral calcinosis with lack of adequate clinical trials, evidence on therapeutic management is limited to observational case series and case reports. The cornerstone of treatment continues to be phosphate lowering through dietary restriction and medications that include acetazolamide, sevelamer, lanthanum, sodium thiosulphate, probenecid, nicotinamide. Anti-inflammatory agents may be used for pain and surgical excision may be offered if the lesions are large with severe restriction of mobility. This systematic review thus attempts to study the outcome of phosphate lowering therapies on pain, lesion size and phosphate levels.

Condition being studied Tumoral calcinosis is a rare clinical syndrome that is characterized by the calcification of periarticular tissue and manifests as swelling around the joints with limitation of mobility. It may be associated with inflammatory bone pain and can cause disability when the lesions are large. There are two variants described – (a) Hyperphosphatemic tumoral calcinosis (HTC) also known as hyperostosis/hyperphosphatemia syndrome in which the calcium levels are normal and the phosphate levels are high and (b) Normophosphatemic tumoral calcinosis in which the calcium and phosphate levels are normal. While HTC is caused by recessive mutations in GALNT3 and Klotho which causes inactivation of FGF 23, a phosphaturic protein, the normophosphatemic variant is caused by mutations in the SAMD protein.

The aetiopathogenesis of the lesions in tumoral calcinosis is attributed to recurrent trauma which leads to haemorrhages. Following this, there is a histiocytic response of foamy macrophages and neobursae formation. In the reparative phase, there is an interplay between multifactorial calcification process and proteolytic cleavage from enzymes released from the degenerating histiocytes. This limits further bursae and bone formation. The main player in calcification is the elevated calcium-phosphate product, driven largely by the prevailing hyperphosphatemia. Finally, there is increase in the calcific debris with arrest of bullae formation and decline in the proteolytic enzyme release from the histiocytes. Fibrosis gradually sets in and results in the lesions that are typical of tumoral calcinosis.
Commonly, affected individuals present with painful masses. The common site of involvement is around the hips followed by the elbows, shoulders, hands, knees and feet. These calcified deposits are composed of calcium hydroxyapatite. There may be local signs of inflammation and a non-specific systemic inflammatory response with fever and elevated inflammatory markers. Dental involvement may occur in the form of obliterated pulp chamber and pulp stone; rarely tumoral calcinosis has also been reported to involve the eyelids and conjunctive.

METHODS

Search strategy Literature Search: A systematic search of the literature published in English language will be performed in keeping with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement. Pubmed, and Scopus, databases will be searched from articles published in 1950s through October 31, 2023 evaluating the outcome of phosphate lowering therapies in individuals with familial hyperphosphataemic tumoral calcinosis.
The following Medical Subject Headings (MeSH) and terms are used in our search strategy; “Tumoral Calcinosis” OR “Hyperphosphataemic Tumoral Calcinosis” AND “Tumoral Calcinosis with hyperphosphatemia” AND “phosphate lowering therapies”.
Eligibility Criteria: All papers published in the English language with a diagnosis of familial hyperphosphatemic tumoral calcinosis, baseline phosphate and treatment outcomes following phosphate lowering therapy will be included. The exclusion criteria comprise studies primarily written in a language other than English, narrative reviews, conference abstracts and patients having secondary causes of tumoral calcinosis.

Participant or population Individuals with hyperphosphatemic tumoral calcinosis.

Intervention Phosphate lowering therapies.

Comparator None.

Study designs to be included Case reports and case series.

Eligibility criteria All papers published in the English language with a diagnosis of familial hyperphosphatemic tumoral calcinosis, baseline phosphate and treatment outcomes following phosphate lowering therapy were included. The exclusion criteria comprised studies primarily written in a language other than English, narrative reviews, conference abstracts and patients having secondary causes of tumoral calcinosis.

Information sources Electronic database: Pubmed, Scopus.

Main outcome(s) Outcomes: Therapeutic response to phosphate lowering therapies; Stability/regression/progression of lesion.

Additional outcome(s) None.

Data management Clinical characteristics, biochemistry and site of lesion will be noted and documented in excel sheet. Analysis of means/proportions will be performed on SPSS.

Quality assessment / Risk of bias analysis All full texts will be read to evaluate the methodological quality of the included cases reports. The authors will use a recently proposed tool, based on the previous criteria from the Pierson, Bradford Hills, and Newcastle Ottawa Scale, and categorized into 4 domains: selection, ascertainment, causality, and reporting. An overall judgement will be made about methodological quality as follows (1: medium; 2: good; 3: very good; 4: excellent).

Strategy of data synthesis Data will beere summarized using descriptive statistics, with means and standard deviations for continuous variables and frequencies and percentages for dichotomous variables. When the data are non-normally distributed, they will be described as median with inter-quartile ranges as appropriate.

Subgroup analysis Will be decided after tabulating data.

Sensitivity analysis Will be decided after tabulating data.

Language restriction English language only.

Country(ies) involved Indian.

Other relevant information None.

Keywords hyperphosphatemic tumoral calcinosis, surgery, sevlamer, acetazolamide, aluminium hydroxide.

Dissemination plans Planned for publication in an Indexed journal of good repute.

Contributions of each author

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