Intramedullary granulomatous lesions. Systematic review of case reports

Lesões granulomatosas intramedulares. Revisão sistemática de relatos de caso

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ABSTRACT

Introduction: Granulomatous inflammation tries to isolate and control a foreign substance considered hard to eliminate. Intramedullary granulomas are rare, but some can be deadly. Objective: To point out the initial reports, differential diagnosis and prognosis of these lesions. Material and Methods: A systematic review related to granulomatous spinal lesions was performed in the PubMed, MedLine (EBSCO), LILACS and Scielo database using the keywords “granulomatous”, “granuloma” and “intramedullary”. Results: Intramedullary granulomatous lesions most commonly are present in the thoracic spine (80% of cases). The most frequent cause of the lesion was tuberculosis, followed by sarcoidosis. Improvement of the symptoms was found in 78%, almost two thirds of this total. Most cases were treated with surgery and medication with 47% of total improvement of symptoms. Sixty seven percent of patients treated only with medications were fully recovered. None of the four patients that were submitted only to surgery fully recovered. Conclusion: Given the most frequent causes are tuberculosis and sarcoidosis, it is suggested to always investigate them. Although the combined treatment was the most used, the drug alone showed greater outcomes. However, more studies are needed to make it possible to confirm the efficacy of those treatments.

Keywords: Intramedullary; Granulomatous; Spinal cord

RESUMO

Introdução: A inflamação granulomatosa tenta isolar e controlar uma substância estranha considerada difícil de eliminar. Granulomas intramedulares são raros, mas alguns podem ser mortais. Este estudo foi realizado com o intuito de apontar as descrições descritas, o diagnóstico diferencial e o prognóstico dessas lesões. Metodologia: Uma revisão sistemática relacionada a lesões granulomatosas da medula foi realizada nas bases de dados PubMed, MedLine (EBSCO), LILACS e Scielo, utilizando como palavras-chave: granulomatoso, granuloma e intramedular. Resultados: Lesões granulomatosas intramedulares estão mais presentes na coluna torácica (80% dos casos). A causa mais frequente da lesão foi a tuberculose, seguida de sarcoidose. A melhora dos sintomas foi registrada em 78%, quase dois terços deste total. A maioria dos casos foi tratada com cirurgia e medicação com 47% de melhora total dos sintomas. Sessenta e sete por cento dos pacientes tratados apenas com medicamentos foram totalmente recuperados. Nenhum dos quatro pacientes que foram submetidos apenas à cirurgia se recuperou totalmente. Conclusão: Sendo a tuberculose e a sarcoidose as causas mais frequentes, sugere-se sempre investigá-las. Embora o tratamento combinado tenha sido o mais utilizado, somente o fármaco apresentou maiores desfechos. No entanto, mais estudos são necessários para tornar possível confirmar a eficácia desses tratamentos.

Palavras-chave: Intramedular; Granulomatosas; Medula espinhal

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INTRODUCTION

Inflammation is the body response to strange bodies (infections) and aggression (tissue lesion). It starts as an acute mechanism, with a quick start and short duration, and the intention of eliminating the source of damage, aggression or infection. In case of no success, the inflammation process continues becoming a chronic mechanism. It is characterized by tissue damage, repairment attempt and mononuclear cells infiltration (each one with different functions). After chronification, the inflammatory process can take different paths, generating different forms, and within these, the granulomatous.

The form of inflammation, characterized by foci of macrophages actives, is a mechanism that tries to isolate and control a foreign substance considered hard to eliminate. Granulomas can still be divided into two types, differing in etiology and pathogenesis: immune and foreign bodies. The first one, caused mainly by persistent infections, is characterized by the T cell immune response which will release interleukins and other cytokines that will perpetuate the response and activate macrophages. Those can still unite with other macrophages, becoming giant multinuclear cells or grow its cytoplasm, becoming epithelioid cells. Foreign bodies granulomas, in the other hand, do not activate T cell-mediated response.

Few conditions cause this pattern, such as tuberculosis, sarcoidosis, Crohn’s disease, and syphilis. But the intramedullary involvement of these lesions is rare.

In order to give a better view of such presentation, this study gathered in the literature, reports of those, analyzing the most frequent causes, spinal levels, demographical proportion (age and gender), treatment opted and outcomes.

MATERIAL AND METHODS

A systematic review relational to granulomatous spinal lesions was performed from February 15 to 17, 2019 in the PubMed, MedLine (EBSCO), LILACS and Scielo databases using as keywords the association of “granulomatous” or “granuloma” and “intramedullary”. The filters “case reports” and “full text” were used to narrow the search.

After removal of duplicates, the authors screened the articles analyzing the following criteria: case reports; full article availability; occurred in human species; and in English, Portuguese, Spanish and French languages. Then, the authors used a modified Jadad’s Scale (Box 1) to select reports. Each article received a 0 to 6 grade (1 point for each positive answer) and only those with 6 points entered the study. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow chart summing the articles selection is exposed below at Figure 1 and the articles included are demonstrated at Table 1.

The search strategy resulted in 66 articles: 47 on PubMed, 8 on Medline, 4 on LILACS and 7 on Scielo database. Of those, 13 duplicates were removed, remaining 53, from which 4 were excluded as “not available”. Other 13 were excluded from the previous 49 because they didn’t fit the proposed criteria. Finally, thirty six articles were included, making a total of forty six cases.

| Question                                      | Yes | No |
|-----------------------------------------------|-----|----|
| The lesion reported is granulomatous?         |     |    |
| The study defined the level of the lesion?     |     |    |
| The lesion was intramedullary?                |     |    |
| The study defined the diagnosis?              |     |    |
| The study exposed the treatment opted?        |     |    |
| The study exposed the outcome of the case?    |     |    |
| Total                                         |     |    |

BOX 1. Modified Jadad’s Scale.
The cases were synthetized using a Microsoft Excel® sheet discriminating: age, gender, lesion location, lesion level, etiological diagnosis, treatment opted and outcomes. Also, gender proportion was analyzed.

In order to analyze the age stratification, the total range (ΔT) was calculated by subtracting the lower limit of the upper. Using one of Milone’s criteria the number of intervals (k) was determined. At the end, the range of classes was defined by dividing ΔT/k:

\[
\Delta T = 70 - 5 = 65 \\
k = \sqrt{n} = \sqrt{\frac{65}{7}} = 6.78 \approx 7 \text{ classes} \\
h = \frac{\Delta T}{k} = 9.28 \approx 10 \text{ years}
\]

The most frequent causes of the lesion were tuberculosis, followed by sarcoidosis, making together a total of 57%. Next to those there were 4 schistosomiases, 3 cryptococcoses, 3 paracoccidioidomycosis, and brucellosis. Other causes include: neurosphilis, cysticercosis, non-Hodgkin lymphoma, histoplasma, pilocytic astrocytoma, acanthamoebas, inflammatory miofibroblastic tumor and multiple cells granuloma.

## RESULTS

Originally the cases were classified into seven age classes with a 10 years range, but in order to better analyze the cases, the authors reduced to 5 classes by uniting some of them. That leaded to the following classes: < 20 years old (4); 20-29 years old (10); 30-39 years (12); 40-49 years (12); and > 50 year-old (10) patients. In general, most of cases occurred on male patients (63%) and there was one transsexual patient.

When divided by age range, male prevalence over female varies: all patients < 20 years were male; 20-29 years, males still prevailed, with a 2.3:1 rate over females; in patients between 30 and 39, the sex distribution was more similar, with 50% of males, 40% females and 10% transsexual patients; in the range 40-49 years there was no incidence difference between genders; and in patients > 50 years old, a 2.3:1 male over female rate was found (Table 2).

| Age range | Mean | Mode | Fm | Fm (%) | Fw | Fw (%) |
|-----------|------|------|----|--------|----|--------|
| 0 | 6.33 (±1.54) | 7 (2) | 3 | 6% | 3 | 6% |
| 10 | 16 (±4) | 16 | 1 | 2% | 4 | 8% |
| 20 | 24.1 (±2.9) | 21, 26 | 10 | 22% | 14 | 30% |
| 30 | 34.1 (±1.79) | 35 (3) | 10 | 22% | 24 | 52% |
| 40 | 43.5 (±3.06) | 40 (4) | 12 | 26% | 36 | 78% |
| 50 | 55 (±2.28) | 57 | 6 | 13% | 42 | 91% |
| 60 | 66.25 (±6.29) | 63, 65, 67, 70 | 4 | 9% | 46 | 100% |
| Total | 37.69 (±15.76) | 40 | 46 | 100% | – | – |

Table 2. Age. Ranges and frequencies.
When divided by age, tuberculosis represented three quarters of cases of patients < 20 years (all male); it also represented the most frequent cause between 20 and 29 years, with 40% of cases (3:1 male over female rate). In patients from 30 to 39 years, tuberculosis was also the most frequent, with the same 40% of cases of the previous category, half of them being male, one quarter female and the other one, transsexual. Between patients of 40 to 49 years, sarcoidosis was most frequent, with 42% of cases (1.5 times more female than males), followed by tuberculosis (33%) with 3:1 male over female. However, patients > 50 years, showed no case of tuberculosis, and sarcoidosis was the most frequent (30%), with two times more male than female ones, followed closely by cryptococcosis and paracoccidioidomycosis, both with 20% and all males (Table 3).

Table 3. Patients with granulomatous spinal lesions: causes, frequencies and gender proportion.

| Diagnosis                     | N (%) | Gender Proportion   |
|-------------------------------|-------|---------------------|
| Tuberculosis                  | 15 (33%) | 73% M / 20% F / 7% T |
| Sarcoïdosis                   | 11 (24%) | 55% M / 45% F |
| Schistosomiasis               | 4 (9%) | 75% M / 25% F |
| Cryptococcosis                | 3 (7%) | 100% M |
| Paracoccidioidomycosis        | 3 (7%) | 67% M / 33% F |
| Brucellosis                   | 2 (4%) | 100% F |
| Cysticercosis                 | 1 (2%) | 100% F |
| Neosyphils                    | 1 (2%) | 100% F |
| Non-Hodgkin lymphoma          | 1 (2%) | 100% F |
| Histoplasma                   | 1 (2%) | 100% M |
| Pilocytic astrocytoma         | 1 (2%) | 100% M |
| Acanthamoebas                 | 1 (2%) | 100% M |
| Inflammatory miofibroblastic tumor | 1 (2%) | 100% M |
| Multiple cells granuloma      | 1 (2%) | 100% M |
| Total                         | 46 (100%) | 63% M / 35% F / 2% T |

The most common reported location of those lesions was in the thoracic spine (80% of cases). There were 15 cases reporting lesions on cervical level and 10 on the lumbar level. Although most frequently in only 1 region, some cases occurred on 2 of the 3 divisions and one even in all three. When divided by age ranges, there was 2 thoracic-exclusive cases and 2 thoracolumbar patients < 20 years, 3 thoracic-exclusive, 3 thoracolumbar, 2 cervicothoracic and 2 cervical-exclusive cases patients from 20 to 29 years. Those patients in the range 30-39 presented 5 thoracic-exclusive, 2 thoracolumbar, 1 cervical-exclusive, 1 cervicothoracic and 1 on all three divisions. In patients from 40-49 years range, 50% presented only on thoracic spine, 25% in thoracolumbar, one sixth in cervical spine and only 1 in cervicothoracic level. Those patients > 50 years, resulted in 50% on thoracic level only, 40% in cervical only and 1 case (10%) presented two lesions, one cervical and the other thoracic.

Of the four patients submitted only to surgery, 2 died due to worsening of the case and the other two had only partial recovery (one with the help of physical therapy). Twelve patients were treated only with medications and 67% of full recovery, one patient with partial improvement, one patient worsened and died and two worsened and then stabilized. Most cases were treated with a combination of surgery and medication (65%) with 83% of cases with total (47%) or partial (36%) improvement of symptoms.

Of the cases analyzed, 78% showed improvement of the symptoms, being almost two thirds of the total. Five patients died on the follow-up (one due to pulmonary infection, one due to chronic renal insufficiency, and the other 4 due to worsening of the case) and three patients had worsening of the case.

CONCLUSION

Based on the cases studied, the immense majority presented lesion on the thoracic portion of the spinal cord, followed by cervical and lumbar. Male patients presented as the majority, with almost two thirds of cases analyzed, as well as adult patients (20-49 years) representing 70% of cases. Given the most frequent causes being tuberculosis and sarcoidosis, it is
suggested to always investigate them. Although most of the patients were treated with both medical and surgical therapy, this review showed that medication only had greater outcomes over those with combined conduct. However, more studies are needed, mainly clinical trials to make it possible to confirm the efficacy of those treatments.

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