

## CASE REPORT

# Anaphylaxis induced by intra-articular injection of chitosan: A case report and literature review

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## Funding information

2020 clinical medicine innovation plan of Jinan science and Technology Bureau, Grant/Award Number: 202019008; 2020 Shandong Province sports medicine integration project cultivation library pilot project, Grant/Award Number: 2020-62; 2021 Shandong First Medical University's research project studying school level education and teaching reform, Grant/Award Number: 2021XY08

## Abstract

Generally, we consider chitosan being a safe, nontoxic natural polymer with wide clinical applications. However, allergic reactions caused by chitosan have been reported on rare occasions. We report here a case of allergy and perform a literature review.

## KEYWORDS

anaphylaxis, chitosan, degenerative osteoarthropathy, intra-articular injection

## 1 | INTRODUCTION

Chitosan is a natural polymer obtained by alkaline deacetylation of chitin, which is the second most abundant polysaccharide after cellulose (Figure 1).<sup>1</sup> Chitosan has a number of special physicochemical properties such

as biodegradability, biocompatibility, hemostatic and antibacterial activity (Figure 2).<sup>2-5</sup> Since chitosan has attracted the attention of scholars all over the world in the medical field, it has been widely used in various biomedical applications, including tissue engineering, wound dressing, cancer diagnosis, and drug delivery (Figure 2),<sup>2</sup>

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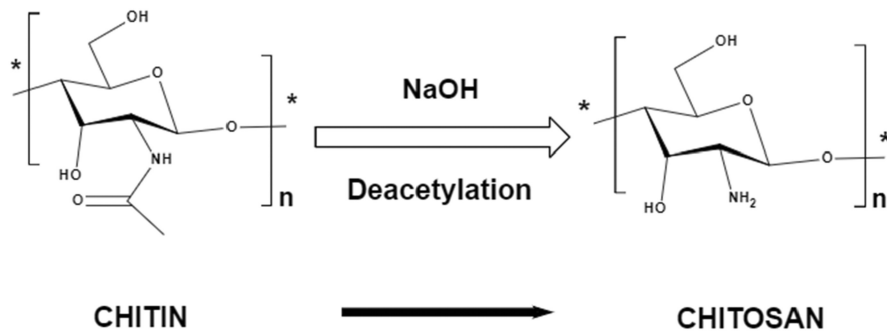


FIGURE 1 Preparation of chitosan.

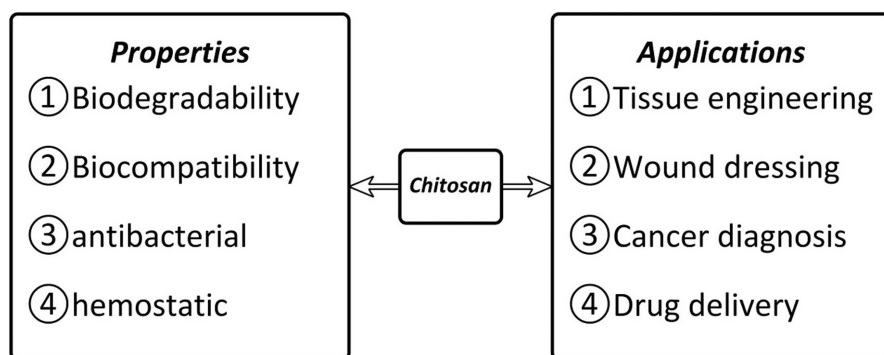


FIGURE 2 Properties and applications of chitosan

but several reports of allergic reactions to chitosan are rare. Herein, we reported a case of anaphylaxis because of intra-articular injection of chitosan. Previously reported cases of chitosan-induced allergy are reviewed as well.

## 2 | CASE SUMMARY

### 2.1 | Case presentation

A 73-year-old man presented to the pain clinic of our hospital for “5 months of left knee pain and mobility impairment.” Physical examination revealed left knee joint swelling, joint space tenderness, and floating patella test (–). Magnetic resonance of the left knee showed degenerative changes in the left knee joint. We diagnosed degenerative osteoarthropathy of the left knee. The outpatient was going to be given medical chitosan [(for intra-articular injection) Shanghai Qisheng Biological Preparation Co., Ltd. production batch number 210971CG1] intra-articular injection of the left knee.

In the outpatient treatment room, the patient was in a supine position, and the skin of the left knee was exposed and elevated. The outer knee of the left knee was selected as the skin puncture point. After the 22G injection needle was punctured into the articular cavity, a small amount of synovial fluid was drawn back, which confirmed that the joint cavity puncture was successful. We slowly injected 2 ml of medical chitosan into the articular cavity. After the injection, the skin and eyes are covered with a Band-Aid.

The puncture and injection process is smooth, and the patient has no discomfort.

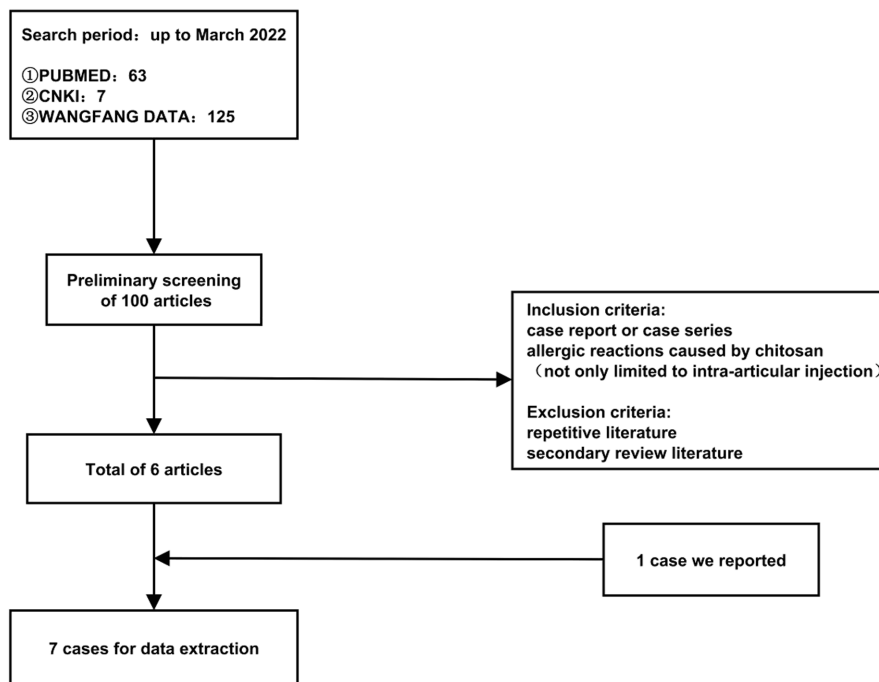
About 5 min after the injection, the patient suddenly experienced dyspnea, cyanotic complexion, convulsions in the limbs, profuse sweating, and self-reported that the pain in the lower back was unbearable. Immediately given supine, oxygen inhalation, ECG monitoring, blood oxygen saturation 98%, heart rate 88 beats/min, blood pressure 146/93 mmHg. We consulted the emergency department physician. Considering the acute drug allergy, give epinephrine 0.5 mg, diazepam 5 mg intramuscular injection, and dexamethasone 5 mg intravenous injection, respectively. The symptoms of the patient gradually eased and completely recovered after 1 h.

We consulted the emergency department physician, considered as acute drug allergy, given epinephrine 0.5 mg, diazepam 5 mg intramuscular injection, and dexamethasone 5 mg intravenous injection, respectively, emergency electrocardiogram: sinus rhythm, occasional premature ventricular contractions. Symptoms were gradually relieved after 20 min of observation and fully recovered after 1 h.

### 2.2 | literature review

According to the inclusion and exclusion criteria (Figure 3), we have comprehensively searched three databases and obtained a total of six articles that meet the criteria. The specific search strategy is shown in Online

**FIGURE 3** Flowchart of the literature review study.



**TABLE 1** Relevant data extracted from

	Number	Ratio(%)
Gender (n = 7)		
Male	3	42.86%
Female	4	57.14%
Age (n = 7)		
<18	1	14.29%
18–44	3	42.86%
44–59	1	14.29%
>59	2	28.57%
Whether there is a clear history of allergies in the past (n = 7)		
Have a clear history of allergies	2	28.57%
No clear history of allergies	2	28.56%
Unknown allergy history	3	42.86%
Routes of exposure (n = 7)		
Prevent intraperitoneal adhesions	3	42.86%
Body cream	2	28.57%
Eat health food	1	14.29%
Intra-articular injection	1	14.29%
Treatments		
Adrenaline	4	57.14%
Antihistamines	1	14.29%
Glucocorticoid	5	71.43%
Stop using relevant cosmetics	2	28.57%
Outcomes		
Good	7	100%

annex 1. The main data extracted from the eligible studies included: the patient's gender, age, allergy history, routes of exposure, clinical manifestations, treatments, and outcomes (Table 1).

In total, we retrieved 195 related articles. We found six articles<sup>6–11</sup> (for a total of seven cases including our case) that reported allergic reactions caused by chitosan, including three males and four females, aged between 10 and 73 years old.

We calculated once for each clinical manifestation, and a total of 33 different clinical manifestations occurred in seven patients. The organs or systems involved in chitosan-induced allergic reaction include skin and mucous membranes, respiratory system, circulatory system, etc. Most patients have multiple systems damaged at the same time. Clinical manifestations include pruritus, urticaria, skin cyanosis, contact dermatitis, etc., in severe cases, anaphylactic shock may occur. See Table 2 for specific clinical manifestations. After symptomatic and supportive treatment, seven patients had a good prognosis and no death.

### 3 | DISCUSSION

Anaphylaxis is a serious systemic hypersensitivity reaction that usually occurs rapidly and can result in death. As a result of anaphylaxis, the airway becomes compromised, posing a potentially life-threatening risk. There may be no apparent skin features or circulation shock when the breathing and/or circulation is affected.<sup>12</sup> The list of agents that can trigger these life-threatening reactions in the population continues to grow. Common

TABLE 2 Clinical manifestations

Organ or system involved	Clinical manifestations(n)	Total number(%)
Skin, mucous membranes and their appendages	Skin cyanosis (1), urticaria (4), pruritus (2), contact dermatitis (2), facial edema (1), cyanosis of complexion (1)	11 (33.3%)
Respiratory system	Dyspnea (3), shortness of breath (2), a lot of pink foamy phlegm (3), scattered dry and wet rales in both lungs (2)	10 (30.3%)
Circulatory system	Tachycardia (3), Hypotension (3), Shock (3)	9 (27.3%)
Other	Convulsions in the limbs (1), profuse sweating (1), unbearable lower back pain (1)	3 (9.1%)

causes of anaphylaxis reactions are medications, foods, insect venoms, vaccines, and latex, with drugs and foods being the most frequent causes. Previous literature has pointed out that the class of drugs that most commonly induce allergic reactions are antibiotics, followed by anti-convulsants.<sup>13</sup> On the contrary, thanks to its remarkable physicochemical properties, chitosan is widely used in tissue engineering and regenerative medicine, especially in bone and cartilage tissue engineering. In the treatment of joint diseases, it is a lubricant in the articular cavity of the bone, suitable for degenerative osteoarthropathy. The main clinical side effects are mostly the leakage of the drug solutions from the articular cavity during injection, resulting in local swelling and transient pain, which can be relieved by themselves. However, there are few reports of allergies caused by chitosan. Our case is an acute allergic reaction 5 min after intra-articular injection of chitosan. So far, there are no similar reports. We consider that the occurrence of allergic reactions is due to the absorption of chitosan into the blood after injection.

Concerning the *in vivo* toxicity profile, it is almost nontoxic for both animals and humans, and LD50 for rats is 16 g/kg.<sup>14,15</sup> In addition, chitosan has achieved FDA-recognized safety status (GRAS) as a wound dressing.<sup>16</sup> Results of a study examining the safety of the Hem Con bandage (made from chitosan) in patients with shellfish allergy showed that<sup>17</sup> of all participants tolerated the bandage with no adverse effects. Similarly, P. J. Zelga et al<sup>18</sup> tested the skin irritation and sensitization of six dressings with different activities and showed that dressings made of chitosan caused little irritation, nor in humans showed severe allergic reaction. These findings may explain that the occurrence of this allergic reaction is not related to its pharmacological toxicity.

In addition, the degree of deacetylation and the size of the molecular weight can significantly influence the physicochemical properties of chitosan.<sup>19–21</sup> Then our attention to the processing and production of chitosan is understandable. The occurrence of this allergic reaction may also be related to the quality of raw materials, production

process, product batch number, or the rapid entry of impurities in drugs into the body as antigen or hapten to stimulate the immune system to produce the allergic reaction. Actually, as early as 2008, the State Food and Drug Administration had issued a “Notice on Strengthening the Supervision and Management of Chitosan Surgical Anti-adhesion Products Manufacturers.” According to the inspection of the quality system of the manufacturers of chitosan surgical anti-adhesion products, four enterprises were ordered to stop production for rectification. It is worth noting that the manufacturers of chitosan used for intra-articular injection in this patient and the prevention of adhesions in peritoneal surgery in the literature review are among them. Therefore, we do not rule out that the manufacturer may have played a certain role in the occurrence of this allergic reaction.

Additionally, the route of administration will also affect the speed and severity of allergic reactions to a certain extent. Common treatment measures for allergic reactions include: staying away from allergens, adrenaline, antihistamines, glucocorticoids, anti-shock treatment, oxygen inhalation or mechanical ventilation, and other symptomatic support treatment. Currently, the relevant international guidelines agree that the first-aid drug for allergic reactions is adrenaline.<sup>12,22,23</sup> This case was the same as the three patients with anaphylactic shock in the literature review. All patients were given epinephrine at the first time, with a good prognosis and no death.

Chitosan is only a small part of what we consider to be “safe” drugs, and allergic reactions such as adenosine, ondansetron have been reported in the literature.<sup>24,25</sup> Therefore, relevant personnel should be prepared for the occurrence of allergic reactions caused by such widely used and considered “safe” drugs in clinical work.

Finally, in the use of chitosan, we recommend that (a) Before medication, you need to ask about the patient's food and drug allergy history in detail. If the patients are allergic to carboxymethyl chitosan or crustacean food such as crabs and shrimps, especially those with

the allergic constitution, they need to be cautious about medication. (b) During medication, chitosan must be injected into the articular cavity. After injection, there is articular fluid, and then push and inject chitosan; If there is blood return during the back pumping, the puncture point shall be changed to re-puncture or the injection shall be stopped to prevent chitosan from entering the blood. (c) After medication, we should pay close attention to the patient's medication response. Once the patient has an abnormal reaction, we should give first aid in time and carry out ECG monitoring if necessary. In particular, the use of adrenaline in allergic reactions should not be hesitant. Moreover, under the premise of strengthening the recognition of the clinical workers on the allergic reaction caused by chitosan, the manufacturers of the source of chitosan production deserve attention.

## 4 | CONCLUSION

To the best of our knowledge, this is the first report describing an acute allergic reaction caused by intra-articular injection of chitosan. Because of the widespread use of chitosan, all clinical workers should strengthen the re-understanding of allergic reactions caused by chitosan and be vigilant about the occurrence of adverse events caused by "safe" drugs. At the same time, chitosan manufacturers are also worthy of attention. Limited by case reports, we still need a large number of samples to confirm the diagnosis, and clarify the relevant mechanism, so as to point out the direction for our clinical work.

### AUTHOR CONTRIBUTIONS

Shengxin Peng and Lei Liu conceived this study. Yuanhao Liang, Wenshan Xiao, Yang Liu, Mengya Yu collected and organized the literature information. Shengxin Peng wrote the manuscript. Lei Liu modified the manuscript. All authors have approved the final manuscript for submission.

### ACKNOWLEDGMENT

All the authors thank the patient for allowing publication of this case study. The authors also thank the anonymous reviewers and editors for their helpful comments on the manuscript.

### FUNDING INFORMATION

2020 clinical medicine innovation plan of Jinan science and Technology Bureau, GRANT / AWARD NUMBER: 202019008; 2020 Shandong Province sports medicine integration project cultivation library pilot project, GRANT / AWARD NUMBER: 2020-62; 2021 Shandong First

Medical University's research project studying school level education and teaching reform, GRANT / AWARD NUMBER: 2021XY08.

### CONFLICT OF INTEREST

The authors declare no conflicts of interests.

### DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article.

### ETHICAL APPROVAL

This case report is a retrospective investigation and not applicable to ethical approval.

### CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Peng S, Liang Y, Xiao W, Liu Y, Yu M, Liu L. Anaphylaxis induced by intra-articular injection of chitosan: A case report and literature review. *Clin Case Rep*. 2022;10:e06596. doi: [10.1002/ccr3.6596](https://doi.org/10.1002/ccr3.6596)