

# Subacute Thyroiditis Presenting as Fever of Unknown Origin

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## Research article

**Keywords:** subacute thyroiditis, fever of unknown origin, de Quervain's thyroiditis, giant cell thyroiditis, granulomatous thyroiditis, pyrexia of unknown origin, SAT, FUO

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# **Subacute Thyroiditis Presenting as Fever of Unknown Origin**

**Title:** Subacute Thyroiditis Presenting as Fever of Unknown Origin

**Running title:** SAT presenting as FUO

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1 **Abstract**

2 **Background:** Subacute thyroiditis (SAT) is a rare but well-established cause of fever of  
3 unknown origin (FUO) and should be considered in the differential of patients presenting with  
4 fever of unknown origin. Few reports in the English literature were published about Subacute  
5 thyroiditis manifesting as fever of unknown origin. Subacute thyroiditis may be hard to detect by  
6 physicians based on history and physical exam if the systemic manifestations are absent.

7 **Methods:** An observational retrospective review of 375 charts of patients presenting with  
8 thyroiditis to the American University of Beirut Medical Center between January 1995 and June  
9 2015. Inclusion criteria included patients who have subacute thyroiditis based on the American  
10 Thyroid Association and American Association of Clinical Endocrinologists guidelines and fever  
11 of unknown origin based on Durak and Street's definition. All patients that do not fit both  
12 inclusion criteria were excluded. The patients' demographics, clinical presentation, laboratory  
13 and diagnostic findings, and treatments used were analyzed.

14 **Results:** 375 charts were reviewed. 31 patients had SAT of which 13 patients had fever of  
15 unknown origin before diagnosing subacute thyroiditis. 13 charts were not available for  
16 screening. Symptoms of hyperthyroidism including palpitations, neck tenderness and weight loss  
17 were not present in all patients. Elevated markers of inflammation mainly ESR and CRP were  
18 raised when screened for.

19 **Conclusions:** The diagnosis of subacute thyroiditis should be considered in patients presenting  
20 with fever of unknown origin and elevated inflammatory markers, even in the absence of  
21 suggestive clinical symptoms.

22 **Keywords:** subacute thyroiditis, fever of unknown origin, de Quervain's thyroiditis, giant cell  
23 thyroiditis, granulomatous thyroiditis, pyrexia of unknown origin, SAT, FUO

## 24 **Background**

25           Subacute thyroiditis (SAT, de Quervain's thyroiditis, giant cell thyroiditis, granulomatous  
26 thyroiditis) as an entity was described before fever of unknown origin (FUO)<sup>1</sup>. It is a rare but  
27 well-established cause of FUO and should be considered in the differential of patients presenting  
28 with the latter. Clinical manifestations include sore throat, fatigue, fever, myalgia, thyroid  
29 enlargement and pain that may radiate to the jaw<sup>1,2</sup>. It frequently follows systemic viral infection  
30 even though no single viral agent has been directly proven to cause this illness<sup>3</sup>. It is a rare entity  
31 and may remain undiagnosed if usual systemic manifestations are absent or atypical<sup>4</sup>. SAT  
32 belongs to the miscellaneous group of diseases that cause classical FUO. This group includes  
33 also other entities: hyperthyroidism, drug fever, factitious fever, deep venous thrombosis and  
34 pulmonary embolism<sup>5,6</sup>.

35           SAT may be hard to detect by physicians based on history and physical exam if the  
36 systemic manifestations are absent. The aim of this article is to highlight the importance of SAT  
37 as part of the differential of FUO even in the absence of systemic manifestations of thyroid  
38 disease. By testing for SAT, healthcare providers may spare the patient additional time, expenses  
39 and diagnostic intervention looking for other etiologies. Another objective is to remind  
40 healthcare providers about the clinical characteristics and laboratory finding relevant to this  
41 entity and contribute to medical literature in an area where little has been published about SAT  
42 and FUO. The available literature, although not very abundant, is mostly in the form of case  
43 reports, while our study is a retrospective chart review that highlights the association between  
44 SAT and FUO.

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47 **Methods**

48 An observational retrospective review of 375 charts of hospitalized patients at the  
49 American University of Beirut Medical Center (AUBMC) with thyroiditis between January 1995  
50 and June 2015 were reviewed. Inclusion criteria were patients that have subacute thyroiditis  
51 (SAT) based on the American Thyroid Association and American Association of Clinical  
52 Endocrinologists guidelines and fever of unknown origin (FUO) based on Durak and Street’s  
53 definition. Patients that did not fit both inclusion criteria were excluded. The patients’  
54 demographics, clinical presentation, laboratory and diagnostic findings, and treatments used  
55 were analyzed. Ethical approval was obtained from the institutional review board committee at  
56 AUB.

57 Literature review was done using Pubmed/Medline, Google Scholar, Scopus, and Science  
58 Direct to search for original articles and review articles published in the English language with  
59 the keywords “subacute thyroiditis”, “fever of unknown origin”, “pyrexia”, “FUO”, “SAT”,  
60 “granulomatous thyroiditis”, “giant cell thyroiditis”, and “de Quervain thyroiditis”. The search  
61 was limited to full-text English language papers and restricted to literature published between  
62 January 2000 to October 2020.

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## 65 **Results**

66 Out of the 375 charts that were reviewed 31 patients had SAT of which 13 patients had  
67 FUO before diagnosing SAT. 13 charts were not available for review [Figure 1]. All results  
68 were summarized in Table 1.

69 The age of patients that were diagnosed with SAT and FUO ranged between 37 and 65  
70 years with a mean age of 50. As for gender distribution 54 % were females. All patients had  
71 fever, and most of the patients had chills (11/12), tachycardia (10/12) and neck pain (9/12) as the  
72 initial presentation. Other less common symptoms were palpitations (7/13), fatigue (6/12), upper  
73 respiratory tract infection preceding presentation (6/13), sore throat (5/11), weight loss (5/12)  
74 and dysphagia (4/12). None of the screened patients had jaw pain.

75 As for inflammatory markers to help suspect SAT in patients presenting as FUO, ESR  
76 was nearly always elevated, in 92 percent of the patients (11/12). CRP was elevated when  
77 ordered (5/5). White blood cell count was elevated on in 46 percent of patients (6/13) with  
78 polymorphonuclear leukocytes predominance. Alkaline phosphatase was elevated in 2 out 8  
79 patients.

80 Of the 6 cases where anti-tyrosine peroxidase and anti-thyroglobulin antibodies were tested for,  
81 only one was positive for both. TSH was suppressed in 11/12 patients. In addition, imaging used  
82 to confirm SAT was thyroid scan and decreased uptake was seen in all patients who performed  
83 the test (10/10).

84 Concerning treatment, all patients were provided with either non-steroidal anti-  
85 inflammatory drugs (NSAIDS) or steroids. 4 patients were treated with NSAIDS. 5 patients  
86 were treated with steroids and 3 patients were treated with NSAIDS initially then shifted to  
87 steroids due to lack of response to treatment. In one patient out of 13 the treatment was not

88 mentioned and follow up not documented. All treated patients had resolution of their symptoms  
89 on follow up.

## 90 **Discussion**

91 FOU was first defined by Petersdorf and Beeson as recurrent fever of three or more  
92 weeks and undiagnosed after one week of hospitalization<sup>4</sup>. The above definition was later  
93 modified by Durack and Street to an unidentified fever of three or more weeks despite three days  
94 of hospitalization or three clinical visits<sup>7,8</sup>. Few reports in the English literature are published  
95 about SAT manifesting as FOU. The most common presentation was neck pain and palpitations  
96 with raised ESR and CRP<sup>1,4,14,15,16,9,10,11,12,13</sup>. However, around one third of cases described in the  
97 literature did not have neck tenderness during the illness<sup>14,15,16</sup>. Persistent fever without neck pain  
98 or thyroid tenderness is an uncommon presentation of SAT and has been rarely described in the  
99 literature as a cause of FOU<sup>17</sup>.

100 FOU is an uncommon but important presentation of SAT. Of our 31 patients diagnosed  
101 with SAT, 42 % presented as FOU. Comparatively, a study done in Saudi Arabia showed that  
102 only 9% of patients with clinical presentation of SAT had FOU before diagnosing SAT<sup>18</sup>. The  
103 mean age at diagnosis of SAT in our study is 50 years in line with previously published data.  
104 Females developed SAT more than males, 54 percent compared to 46 percent respectively.  
105 However, published data shows that females are 3 to 5 times more likely to have SAT than  
106 males<sup>16,11,19</sup>. As found in the literature, many symptoms of SAT were present in the studied  
107 patients including fever, chills, tachycardia, fatigue and preceding viral upper respiratory tract  
108 infection. Neck pain which is usually present in more than 90% of patients with SAT<sup>11</sup>, was only  
109 present in 75 percent of the patients presenting with FOU and SAT. The latter may have played a  
110 role in delaying diagnosis.

111 Elevated ESR and CRP are important markers to help suspecting SAT. They were  
112 elevated in almost all our patients. Several studies have mentioned alkaline phosphatase being  
113 usually elevated in patients with SAT<sup>5,16,11,19</sup>. In our study one in four of screened patients had an  
114 elevated alkaline phosphatase, which makes it an important marker when screening for SAT in  
115 setting of FUO. TSH was suppressed in almost all cases. Thyroid scan was able to confirm all  
116 cases of SAT presenting as FUO by having minimal uptake. A recent study mentions PET CT  
117 scan as a possible detector of painless SAT by showing high focal or elevated diffuse uptake in  
118 the thyroid<sup>8</sup>. This method was not used in the reviewed cases.

119 Treatment used consisted of NSAIDs, steroids or steroids following failure of NSAIDs  
120 like what was previously published<sup>20,21</sup>. To note that 25 % of our patients did not initially  
121 respond to NSAIDs favoring the use of steroids as the drug of choice in patients presenting with  
122 FUO and found to have SAT refractory to NSAIDs. In fact, one study showed superiority of  
123 steroid use in SAT in patients who fail to achieve clinical remission with NSAIDs<sup>22</sup>. Long term  
124 follow-up of patients presenting with SAT is needed to assess for development of permanent  
125 hypothyroidism which may occur post transient thyrotoxicosis in around 25 percent of patients  
126 requiring treatment with levothyroxine<sup>23</sup>.

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## 128 **Limitations**

129 The limitation of our study is in its retrospective nature and representing only the  
130 experience of one medical center. Given the fact that many cases of SAT and fever are usually  
131 diagnosed in ambulatory setting, it will be very difficult to determine the true role of SAT in  
132 FUO. In addition, long term follow-up through chart review was not possible to determine long  
133 term consequences of SAT.



134 **Conclusion**

135 FOU is a diagnosis of exclusion that encompasses a wide spectrum of disorders. When a  
136 patient is presenting with FOU, SAT should be considered as part of the differential, even if  
137 there are no suggestive clinical symptoms especially in the setting of elevated markers of  
138 inflammation. Initial workup should include thyroid function tests even if no signs and/or  
139 symptoms are suggestive of hyperthyroidism, and alkaline phosphatase.

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## 157 **Abbreviations**

- 158 - CRP: C-reactive protein
- 159 - ESR: Erythrocyte sedimentation rate
- 160 - FUO: Fever of unknown origin
- 161 - SAT: Subacute thyroiditis
- 162 - NSAIDs: Non-steroidal anti-inflammatories
- 163 - TSH: Thyroid stimulating hormone
- 164 - URTI: Upper respiratory tract infection

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## 166 **Declarations**

### 167 **Ethics approval and consent to participate**

168 Approval from the American University of Beirut Medical Center (AUBMC) Institutional  
169 Review Board (IRB) was obtained, along with consent from each patient before accessing their  
170 medical records. The IRB protocol number is: IM.AR-B.10. For further inquiries, contact  
171 [irb@aub.edu.lb](mailto:irb@aub.edu.lb). Contact information for the members of the ethics committee is available at  
172 <https://www.aub.edu.lb/irb/Pages/contactus.aspx>.

### 173 **Competing interests**

174 The authors hereby declare that they have no conflicting interest.

### 175 **Data Availability**

176 Anonymous data is available upon request

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178 The authors declare that no funding was received for their work.

### 179 **Author contribution**

180 Dr. Abir Bou Khalil contributed to the writing of the manuscript, and data collection and  
181 analysis.

182 Dr. Walid Alam contributed to the writing and review of the manuscript.

183 Dr. Abdul Rahman Bizri contributed to the writing and final revision of the manuscript.

184 *All authors have read and approved the manuscript.*

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186 Not applicable.

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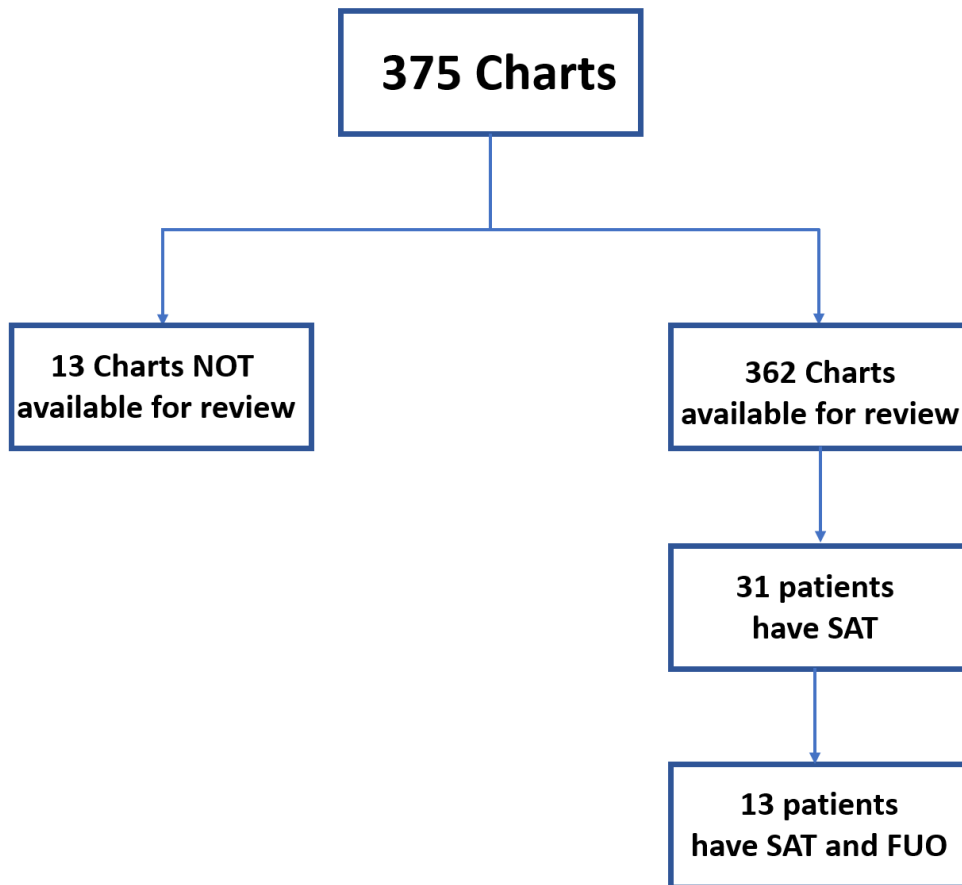
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205 *Figure 1.* Results of retrospective chart review.

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214 **Table 1.** Characteristics and clinical details of patients with SAT and FUO.

<b>Number of Patients (N)</b>	<b>13</b>
<b>Demographics:</b>	
Mean Age	50
Female Gender	7 (54%)
<b>Signs and Symptoms:</b>	
Fever	13 (100%)
Tachycardia	10/12 (83%)
Chills	11/12 (92%)
Neck Pain	9/12 (75%)
Fatigue	6/12 (50 %)
URTI <sup>1</sup> History	6/13 (46 %)
Sore Throat	5/11 (45%)
Weight Loss	5/12 (42%)
Dysphagia	4/12 (33%)
<b>Pertinent Laboratory Findings:</b>	
Low TSH <sup>2</sup>	11/12 (92%)
ESR	11/12 (92%)
CRP	5/5 (100%)
Elevated WBC <sup>3</sup> Count	6/13 (46%)
Elevated Alkaline Phosphatase	2/8 (25%)
<b>Imaging:</b>	
Thyroid Scan decreased uptake	10/10(100%)

<sup>1</sup> Upper respiratory tract infection

<sup>2</sup> Thyroid stimulating hormone

<sup>3</sup> White blood cells

<b>Treatment Used:</b>	
NSAIDS <sup>4</sup>	4/12 (33%)
Steroids	5/12 (52%)

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<sup>4</sup> Non-steroidal anti-inflammatories

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# Figures

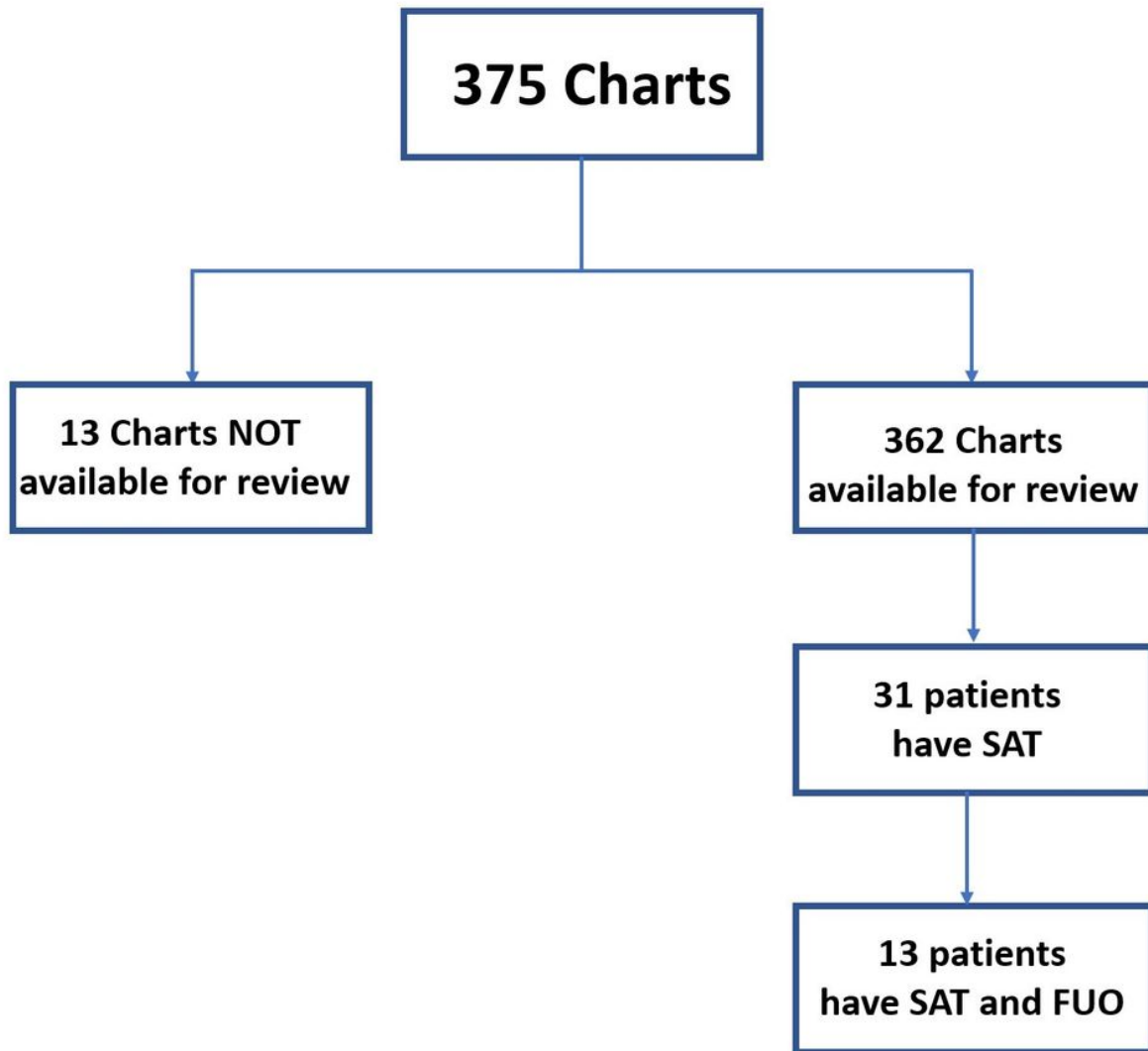


Figure 1

Results of retrospective chart review.