



## Infectious Nosologies and Tumoral Fever, A Crucial Alliance

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### Abstract

**Background:** The importance of early detection and diagnosis of malignant pathologies is well known [1,2]. It gets even more important, a necessity indeed, when fever is the dominant or the only symptom or when microbial agents are isolated.

**Material:** The study included 131 cases, admitted at the Infectious Disease Hospital during 1980-2010, age-group 35 - 70 yrs old. Fever represented the dominant or the only symptom related to 17 different types of tumor pathologies.

**Methods:** We built the etiological and nosologic structure of infectious pathologies [3] that resulted to be wrong diagnoses associated to the presence of a tumor pathology [4,5]. We also made evidence of clinical and laboratory data that contributed in these misdiagnoses.

**Results:** Infectious Wrong Diagnoses: Brucellosis: 13 cases with recurrent fever, sweats, joint pain, 9 cases seropositive for Brucella - Diagnosed Tumor: renal carcinoma 2; PNET 1; metastasis 3; lymphoma 3; mesothelioma 1, Hepatocellular Carcinoma (HCC) 1, gastric 1, seminoma 1. Sepsis: 39 cases with continuous /high fever tachycardia; tachypnoea; leucocytosis; 13 positive blood cultures (S.aureus 7, S.epidermidis 5, Sh.sonnei 1) - Tumors: Acute Lymphoid Leucosis (ALL) 1, HCC 3, renal 2; adrenal 1, biliary tract 2; leucosis 5; lymphoma 4; metastasis with no primary focus 5, mixoma 1. Leishmaniasis: 10 cases with intense/high fever, asthenia, weight loss, hepatosplenomegaly; 4 seropositive cases - Tumors: HCC 1, gastric 1, metastasis 1, Chronic Myeloid Leucosis (CML) 1, Hairy Cell Leucosis (HCL) 1, lymphoma 5. Toxoplasmosis: 13 cases with continuous/moderate fever, lymphadenopathy, sweats; 7 seropositive cases - Tumors: Non Hodgkin Lymphoma 12, gastric 1. Typhoid fever: 18 cases with continuous fever, hepatosplenomegaly; 5 cases with positive Vidal - Tumors: HCC 5, colon 4, gastric 3; splenic lymphoma 1, ALL 3, CML 2. Dysenteric syndrome: 9 cases with mucus bloody diarrhea and 6 with positive microbial agents (shigella 2, salmonella, trichuris, 1, ascarids 1, entamoeba 1) - Tumors: colon 5, prostatic 1, uterus 2, ovarian 1. Influenza: 2 cases with continuous/high fever, toxicosis, upper respiratory syndrome - Tumors: thyroid cancer 1, bronchial 1. Tonsillopharyngitis: 3 cases with hyperpyrexia, odinophagia, difficulty in speaking and positive cultures: S.aureus 1, S.βhemolytic 2. - Tumors: thyroid cancer 1, ALL 2.

**Conclusion:** 1. Tumor fever was associated with clinical syndromes which strongly suggested an Infectious disease in 83% of cases. 2. We encountered positivity for infective agents in 35.87% of cases with tumor fever. 3. Misdiagnosis was related in all cases with the microbiologic and serologic proof of Infectious Diseases.

**Keywords:** Tumor Fever; Infectious Nosologies; Misdiagnosis

### Introduction

Fever remains the most important clinical feature related to infectious diseases. Different patterns of fever, history clues, labora-

tory and imaging data are essential in building an "Infectious identikit" which remains the very first cause of fever that is traditionally excluded [6,7]. However, everyday clinical practice has shown that

fever can be the principal or even the only symptom of malignant pathologies too [8,9].

The mechanisms by which malignancies induce fever are not fully understood. The release of pyrogenic cytokines either directly from tumour cells or from macrophages responding to tumour are likely to play a major role, particularly interleukin (IL)-1, IL-6 and tumour necrosis factor (TNF) $\alpha$ . Cytokines induce prostaglandin E2 which acts on the hypothalamus, causing a change in the thermostatic set point [10,11].

If we see it under this optic, it is oversimplified, considering that fever is a clear and strong indicator of the adaptive host immune response against different challenges, infectious ones or not.

Unfortunately there is no fever pattern pathognomonic of cancer which can lead clinicians towards a tumor pathology. There are several clues that can be helpful during the diagnostic triage; classically, tumor fever may be less associated with rigors, or hemodynamic changes (tachycardia and hypotensive episodes). Therapeutic response indicates that fevers is not affected by the use of antimicrobials, it is only partially relieved by paracetamol and may respond better to nonsteroidal anti-inflammatory drug (Naproxene Test). Other suggestive clinical signs serve to fulfill the diagnostic frame like: night sweats, anorexia and significant weight loss, lymphadenopathy, especially for Hodgkin's or non-Hodgkin's lymphoma. Fullness sensation in the left upper quadrant may indicate splenomegaly, which can be associated to chronic myelogenous leukemia or disseminated lymphoma [12,13,14].

Nevertheless, the etiological diagnosis of fever is based on laboratory and imaging evidence. Ironically, the microbiological and serological proof which is much expected from the clinicians to reach a diagnose, has often become the cause of misdiagnosis for patients which are admitted as Fever of Unknown Origin [15,16].

This article tends to raise the concern of wrong diagnoses related to the presence of these "pseudoinfections" and possible solution by making evidence of possible matches between infectious pathologies and tumors related to them [17].

## Material

The study included 131 patients hospitalized at the Infectious Diseases Service during the 5-year period from 2011-2016. age-group 35-70 yrs old.

Fever represented the dominant or the only symptom referred by the patients. Patients presenting specific symptoms suggesting a possible infectious syndrome that could generate a febrile syndrome were excluded from this survey.

## Method

The patients included in this were equipped with the:

1. Epidemiological survey [18,19,20].
2. Anamnestic, and clinical assesment
3. Biological / biochemical examination;
4. Algorithms of etiologic diagnosis (microbiological investigations such as hemocultures, coproculture, uroculture, tampon cultures from various inflammatory sites, serodiagnostic research such as Vidal, Wright, Weil-Felix, Toxoplasma Gondii Elisa)
5. Imaging - radiological, eco, ct, RMI searches.

The above mentioned data/tests were applied to the patients rationally according to epidemiological, clinical, biological and imagery criteria.

We built the etiological and nosologic structure of infectious pathologies that resulted to be wrong diagnoses associated to the presence of a tumor pathology. We also made evidence of clinical and laboratory data that contributed in these misdiagnoses.

## Results

131 patients underwent a diagnostic protocol in order to reach an etiologic diagnosis. Epidemiological, clinical and biological data were crucial in establishing a prompt presumptive diagnosis which was confirmed with further specific exams. We encountered 8 Infectious Pathologies responsible for the misdiagnoses and 17 corresponding tumor pathologies. Infectious pathologies: Brucellosis: 13 cases with recurrent fever, sweats, joint pain, 9 cases seropositive for Brucella - Diagnosed corresponding tumor: renal carcinoma 2; PNET 1; metastasis 3; lymphoma 3; mesothelioma 1, Hepatocellular Carcinoma (HCC) 1, gastric 1, seminoma 1. Sepsis: 39 cases with continuous /high fever tachycardia; tachipnoe; leucocytosis; 13 positive blood cultures (S.aureus 7, S.epidermitis 5, Sh. sonnei 1) - Tumors: Acute Lymphoid Leucosis (ALL) 10, HCC 3, renal 2; srenal 1, biliary tract 2; leucosis 5; lymphoma 10; metastasis with no primary focus 5, mixoma 1. Leishmaniasis: 10 cases with intense/high fever, asthenia, weight loss, hepatosplenomegaly; 4 seropositive cases - Tumors: HCC 1, gastric 1, metastasis 1, Chronic Mieloid Leucosis (CML) 1, Hairy Cell Leucosis (HCL) 1, lymphoma 5. Toxoplasmosis: 13 cases with continuous /moderate fever, lymphadenopathy, sweats; 7 seropositive cases - Tumors: Non Hodgkin Lymphoma 12, gastric 1. Typhoid fever: 18 cases with continuous fever, hepatosplenomegaly; 5 cases with positive Vidal - Tumors: HCC 5, colon 4, gastric 3; splenic lymphoma 1, ALL 3, CML 2. Dysanteric syndrome: 9 cases with mucus bloody diarrhea and 6 with positive microbial agents (shigela 2, salmonella, trichuris, 1, ascarids 1, entamoeba 1) - Tumors: colon 5, prostatic 1, uterus 2, ovarial 1. Influenza: 2 cases with continuous /high fever, toxicosis, upper respiratory syndrome

-Tumors: thyroid cancer 1,bronchial 1.Tonsillofaringitis:3 cases with hyperpirexia, odinophagia, difficulty in speaking and positive cultures: S.aureus1, S.β hemolitik 2.- Tumors: thyroid cancer 1,ALL2.

Nr	Diagnose	Nr.Of Cases	Clinical Signs	Positive Proof Of Microbial Agent	Corresponding Tumor	M/F Ratio	Median Age
1	Brucellosis	13	recurrent fever, sweats, joint pain	9 seropositive	renal carcinoma 2; PNET 1; metastasis 3; lymphoma 3; mesothelioma 1, (HCC) 1, gastric 1, seminoma 1	3:1	45-54
2	Sepsis	39	continuos /high fever tachicardia ; tachipnoe	13 positive blood cultures S.aureus 7, S.epidermitis 5, Sh.sonnei 1	ALL 10, HCC 3, renal 2; surenal 1, billiary tract 2; leucosis 5; lymphoma 10; metastasis 5, mixoma1	1:1	25-34 45-54
3	Leishmaniasis	10	intense/high fever, asthenia, weightloss, hepatosplenomegaly	4 seropositive cases	HCC 1, gastric 1, Metastasis 1, CML 1, HCL 1, lymphoma 5	2:1	25-34
4	Toxoplasmosis	13	Continous /moderate fever, lymphadenopathy, sweats	7 seropositive	NHL 12, gastric 1	1:2	25-34
5	Typhoid Fever	18	continuos fever, hepatoslenomegaly	5 positive Vidal test	HCC 5, colon 4,		
6	Dysanteric Syndrome	9	mucus bloody diarrhea	shigela 2, salmonella 1 trichuris 1 ascarids1 enthamoeba1	colon 5, prostatic 1, uterus 2, ovarial 1	2:1	25-34 55-64
7	Influeza	2	continuos/high fever, toxicosis, upper respiratory syndrome	1 seropositive	thyroid cancer 1, bronchial 1	1:1	35-44
8	Tonsillofaringitis	3	hyperpirexia, odinophagia, difficulty in speaking	S.aureus1, S.βhemolitik 2	thyroid cancer 1, ALL 2.	1:1	25-34

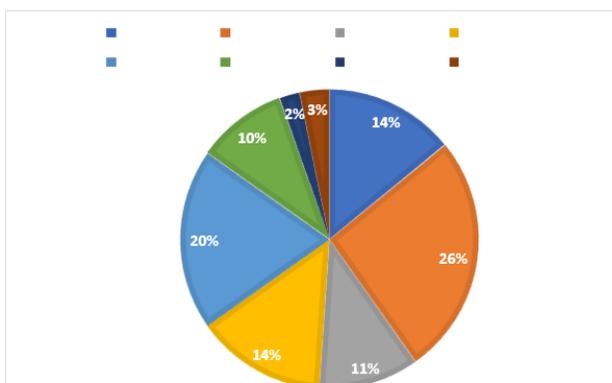


Table 1

## Discussion

Undifferentiated febrile illnesses represent an old and everlasting issue for the clinicians. Usually, in clinical practice, fever is empirically related in the first place with an infectious disease. Aiming the rapid etiological diagnoses, the clinicians apply wide range protocols, correlated with specific epidemiological, anamnestic and clinical indicators in each patient [21,22].

Meantime, we tend to explore as much as possible the possible causes of the febrile illness. In order to achieve as many answers as possible for our diagnostic dilemma, several laboratory and imaging examination are performed.

The results evidenced above look particularly interesting and a novelty in terms of Febrile syndrome investigation [23,24,25].

We encountered 8 different infectious pathologies which coexisted with tumor pathologies, leading in this way to misdiagnoses.

Brucella, a zoonosis strongly indicated as a possible causes of FUO in Albanian adults is related to 8 different types of tumors. Lymphoma and metastasis with no primary focus showed a moderate dominance compared to other malignances.

Sepsis encountered for most of infectious diagnoses (29.7%). we evidenced a correlation with 9 type of tumors; major part acute leucosis and lymphoma.

Leishmaniasis and Toxoplasmosis both demonstrated similar clinical patters and associated tumor pathologies, lymphoma in major part.

Typhoid fever showed a diverse spectrum of tumor pathologies The digestive tract was affected with 72% of tumors, mainly affecting the liver, colon and stomach.

Dysanteric syndrome evidenced significant clinical and microbiological data and is strongly related to colon cancer.

Both influenza and tonsillopharyngitis modestly showed us that significant clinical and microbiological evidence can lead to considerable number of misdiagnosis.

Rapid diagnosis in cases with Undifferentiated Febrile Illnesses remain the principal aim of the diagnostic triage progress. Assuming that tumor fever represent a consistent part of the Febrile Syndromes, our mission becomes even more important an crucial. A delayed diagnosis would signify loosing precious time for the patient but also exposure to unnecessary different types of therapeutic regimens.

Furthermore, we would face enormous diagnostic and therapeutic cost and still remain in diagnostic dilemma.

The results of our study tend to highlight the wide and colorful optic of febrile illnesses. It is important to be broad minded and to consider all the possible diagnostic options, deriving from the patient epidemiological, clinical and laboratory patterns.

## Conclusions

1. Tumor fever represent a consistent part of Febrile Illnesses.
2. Our study evidenced that tumor fever was associated with clinical syndromes which strongly suggested an Infectious disease in 83% of cases.
3. We encountered positivity for infective agents in 35.87% of cases with tumor fever 4. Misdiagnosis was related in all cases with the microbiologic and serologic proof of Infectious Diseases.

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