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1 **Some undesirable traps which can mislead the pathologist...**

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16

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22 **Abstract**

23 In clinical laboratories, the diagnosis of parasite diseases can sometimes be challenging for non-expert
24 microbiologists. Indeed in spite of the advent of the molecular biology, macro- and microscopic
25 examination still remains essential. Nonetheless, it is usually not automated and requires great skills to
26 complete the correct diagnosis. It is not infrequent that inert elements mislead to erroneous diagnoses.
27 Through three different concrete examples, this article aims at underscoring the actual risk of parasite
28 misidentification and at highlighting the systematic approach to be conducted in order to enable
29 reliable diagnosis.

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31 **Keywords:** rice-bodies, ciliocytophthoria, starch grains

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44 **Introduction**

45 In clinical laboratories, the diagnosis establishment of parasite diseases can be challenging for
46 pathologists or non-expert microbiologists. Thorough macro- and microscopic observation and
47 histological examination of miscellaneous biological specimens, such as bronchial-alveolar lavage
48 fluids (BALF), feces or biopsies of various natures, are the key-steps for reaching an accurate
49 diagnosis. So far, these methods have been usually non-automated yet and both require extensive
50 experience. Misidentification pitfalls are numerous, and pathologists or microbiologists should always
51 be aware of them to avoid failure in the diagnosis process. Indeed, several inert or non-pathogenic
52 elements can frequently mislead to erroneous diagnoses, and thus subsequently to inadequate curative
53 therapies. Diagnostic difficulties are primarily emphasized when managing a patient who is used to
54 live or has lived in tropical areas; the imported diseases are often neglected, and thus the pathologists
55 and microbiologists are less seasoned with them and their diagnosis.

56 Therefore to reinforce the accuracy of their diagnostic conclusions, all laboratory staff should be
57 informed of few very-practical tricks to enable better recognition of pathogenic elements and for
58 distinguishing them easily from non-parasite structures. In this article, we will expose three concrete
59 examples that focus on thorough observations of fake parasites in biological samples, and we will
60 discuss more the differential diagnosis for each one.

61

62 **Maggots or cestode vesicles?**

63 A 58-year-old woman underwent a total left hip replacement due to coxarthrosis. In the following
64 months, she began to feel chronic pain next to the joint, in spite of the painkiller medications. No
65 clear etiology was found through the magnetic resonance imaging (MRI). Likewise, a puncture was
66 not contributive. Twenty-two months after the initial surgery, the hip prosthesis was removed in order
67 to avoid a septic issue. During this second intervention, numerous little white inert bodies,
68 measuring seven to eight millimeters in length, were found around the soft tissues (Figure 1 A) and
69 above the prosthesis (Figure 1 B). The samples – which look like maggots or cestode vesicles at first
70 glance – were sent to the hospital laboratory for parasite identification (Figure 1 C), but were finally

71 characterized as rice-bodies. The *in vitro* bacterial culture of the tissue surrounding the rice-bodies
72 eventually isolated *Cutibacterium acnes* colonies, *i.e.* natural saprophyte bacterium of the skin,
73 whereas the mycological culture remained sterile. Based on periodic acid Schiff (PAS) and
74 hematoxylin and eosin safron staining, the histopathological examination showed fibrin deposition
75 with inflammatory cells, but no parasite. To definitively exclude cysticercosis, the research of *Taenia*
76 *solium* antibodies was conducted, but was found negative. A second total hip replacement was
77 programmed, four months later. No complication occurred, and the patient left the hospital with
78 favourable outcome.

79

80 **Ciliated protozoans?**

81 A 65-year-old woman underwent surgical resection of womb fibroma that was evolving over one
82 year. There was no known underlying infection at time of the surgery. Concomitantly to the
83 intervention, aspirate of the peritoneal liquid was systematically addressed to the hospital laboratory
84 for biological investigations. At the fresh mounting examination, several mobile structures of 10-25
85 μm were observed. At higher magnification, they appeared ciliated on their whole circumference
86 (Figure 2 – video 1), a little bit like a protozoan. However, the motions were quite unnatural, depending
87 mostly on the Brownian flow. Finally, these structures were identified as ciliocytophthoria artifacts
88 coming from uterine tubes or endometrium. No *in vitro* cultures were positive. There was no
89 complications for the patient and no occurrence of infection. The outcome was favourable.

90

91 **Segmented helminth?**

92 A 58-year-old male was found dead at home and subsequently autopsied by forensic scientists for
93 suspicion of COVID-19 (coronavirus infectious disease – 2019) infection. During necropsy, some lung
94 lesions were clearly observed, and biopsies were then performed for further investigations.
95 Histopathology examination confirmed the presence of foci of acute pneumonitis. Moreover, several

96 unusual round- or oval-shaped structures, with size ranging from 2-3 μm to 10-15 μm , were noticed
97 within the lumen of alveoli and bronchioles (Figure 3). Due to the size and the regular section,
98 helminth larvae or nematode remnants were first suspected. However at higher magnification, the
99 appearance was rather suggestive of starch grains. The grains had been probably unintentionally
100 aspirated into the lungs, and thus were not assumed to be responsible for the death. The latter was
101 finally inferred to a stroke.

102

103 **Discussion**

104 Correct identification of parasites in clinical samples can be critically challenging, including for quite-
105 skilled microbiologists. The latter have to conduct a systematic thorough approach during the macro-
106 and microscopic examination of all the specimens that are addressed to them. Indeed, the risk of
107 confusion can be really detrimental in some circumstances.

108 Regarding the first case, one could have first suggested vesicles due to any cestod infection, *e.g.*
109 cysticercosis, when facing the oval white structures. However in the medical history of the patient,
110 there were no clear clues that could have reinforced this diagnostic hypothesis. In contrast, the
111 observation was finally more in adequation with rice-bodies description.[1, 2] Rice-bodies appear
112 rubbery when cut into pieces, and they are theoretically not hollow. However, there contain neither
113 liquid nor parasite elements, wether living or dead, inside. Rice-bodies are rarely observed; they
114 sometimes form during inflammatory processes of the synovial liquid, like infectious arthritis,
115 rheumatoid arthritis, non-specific arthritis or osteoarthritis.[3] The pathogenesis may be explained by
116 microinfarcted synovium and release of tissue into the joint, and subsequent encasement by fibrin
117 deposition.[4] Another hypothesis suggests a *de novo* formation in synovial fluid independently of any
118 synovial elements, and progressive enlargement with aggregation of inflammatory nodules consisting
119 of fibrin, collagen, inflammatory cells and blood vessels.[5] In the present case, the rice-bodies
120 probably developed after the first hip surgery. Usually, rice-bodies are isointense on T1-weighted MRI

121 and slightly hyperintense on T2-weighted MRI relative to muscles;[6] but in the present case, rice-
122 bodies were unperceivable during medical imaging.

123 At first glance, the second observation reported herein could have suggested a vegetative stage of
124 ciliated protozoans,[7] like trichomonids or paramecia.[8] Actually, the microscopic structures were
125 rather consistent with ciliocytophthoria artefacts.[9] Ciliocytophthoria are usually the result of the
126 degenerative process of ciliated cells consequently to various common infections, like miscellaneous
127 virus diseases.[10] They are produced from the triangular top part of the bronchial or uterine cells, at
128 the luminal border, which is separated from the cytoplasm bearing the decaying nucleus.
129 Ciliocytophthoria size is quite variable. The cilia are straight, sometimes only represented on a limited
130 part of the outer perimeter, and have a uniformed short length. They express a coordinate and
131 synchronous rhythmic beating which does not lead to any active movement.[11] All these features
132 should theoretically allow a clear distinction with (non-)pathogenic flagellated or ciliated protozoans.
133 For example, the vegetative stage of *Giardia duodenalis* displays a flat pear-shape with two
134 transverse, claw-shaped median bodies, and with four pairs of flagella. *Lophomonas blattarum* bears
135 irregular long flagella arising over the anterior part, and which are longer at center and shorter at
136 sides.[11] Furthermore, the motility of flagella is much more active.[12] Among the ciliate phylum,
137 *Balantioides coli* trophozoites are large, up to 150 µm in length, and their entire cell surface is covered
138 by short cilia.[13]

139 The third case about the observation of starch grains highlights how histopathology examination can
140 be tricky for pathologists and parasitologists. Starch grains are quite common structures. Their
141 morphologic presentation is the same for all vegetables; they are stained in dark pink color by the PAS
142 method, which indicates high concentration in carbohydrates. Starch grains contain a lobulated and
143 empty internal part with no clear well-defined structures inside, and there is a lack of inflammatory
144 response surrounding these exogenous particles.[14] The presence of such starch particles has already
145 been described in inhalation pneumonia,[15] but with no clear demonstration of any pathogenic role.
146 Likewise, starch grains may be sometimes confused with pinworm remnants. However, *Enterobius*
147 *vermicularis* pinworm is quite different, regarding its morphology: the transversal section of its body

148 displays a pair of cuticular crests. Usually, it also shows typical eggs in the uterus and the
149 characteristic narrow meromyarian layers (two to three muscle layers *per* quarter section divided by
150 four cords).[16]

151 In conclusion, in case of any doubt about the parasite etiology, the clinical specimens have to be
152 systematically addressed to the parasitology laboratory in parallel before the tissue fixation which is
153 mandatory for histological examination, and in order to get a specialized advice on a fresh sample.
154 Although the multiplex real-time PCRs have been increasingly used as first-line diagnostics,[17] the
155 macro- and microscopic examination still play a major role in the diagnostic process. The three
156 aforementioned cases show how numerous can be the pitfalls leading to erroneous identification. In
157 such a context, one should remember that the microbiologists own a critical expertise added to an
158 habit of systematic approach of biological analysis.

159

160 **Ethics**

161 The patients were informed and did not oppose to the publication process. As the study is retrospective
162 with no impact on the routine healthcare, no specific approval was required by the authorities.

163

164 **Conflict of interest**

165 None

166

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200

201 **Figure legends**

202 Figure 1: Rice-body elements. A) Dissection of the left hip compartment showing multiple
203 surrounding white bodies. B) Same hip after removing the superficial white bodies. C) Numerous rice
204 body-like structures removed from the hip prosthesis.

205

206 Figure 2: Observation of ciliocytophthoria particles at the fresh mounting examination x400.
207 Ciliocytophthoria artifacts are degenerated from bronchial cells and each one is constituted by the
208 nucleus (nc) with small cytoplasm that bears the cilia (ci). The latter arise from the terminal bar (tb).

209

210 Figure 3: Histological observation of starch grains (sg) within the lumen of bronchioles at time of
211 necropsy A) Hematoxylin and eosin (H&E) stain x125; B) Grocott-Gomori's methenamine silver
212 (GMS) stain x125; C) H&E stain x250, showing more clearly a lobulated and optically empty
213 internal part (‡); D) Periodic acid Schiff (PAS) stain x250, indicating the high concentration in
214 carbohydrates of the particle through the dark pink colour.

215

- 216 Video 1: Observation of ciliocytophthoria particles at the fresh mounting examination x400. Note the
- 217 unilateral disposition of the cilia and the unnatural movements of their beating.