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Review Article

Chasing the Zebras: choosing Between the One, the Many, and the Pursuit of Knowledge -

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ABSTRACT

Introduction: A physician plays many roles: that of a caring clinician, an objective scientist, and a curious and critical investigator. Upon discovery of a pathology that is particularly unusual, choosing between these roles can be particularly difficult.

Methods: We introduce an unusual case that prompted significant ethical debate among the team of physicians caring for the patient, as confirmation of the suspected disease process would potentially require unnecessary and arguably harmful intervention that was unlikely to change management or prognosis. Using a review of the literature and references to historical documents, we launch a discussion of the ethical dilemmas surrounding situations like these, namely weighing academic interest and potential benefit to the medical community and future patients against the risk of harm to patients, whose health we have vowed to protect.

Results: Several options were considered, but the care team agreed that any invasive testing had the potential to do more harm than good to the patient's health; despite an increased possibility of a false-negative result, a superficial biopsy was ultimately considered and suggested to the patient instead, although she was informed that it would only provide information and was unlikely to alter her poor prognosis. Its findings were consistent with the suspected diagnosis, and the patient was pleased to learn that she was able to further advance medical knowledge and potentially help future patients.

Conclusions: Doctors are often faced with complex and difficult decisions and have to be prepared to face a variety of ethical dilemmas on a regular basis. The commonness of these dilemmas, however, does not make them any less complex or difficult to work through. It is important to consider and value the pursuit of knowledge and the good of the many in any of these situations; but patients' best-interest and autonomy should always be addressed and incorporated in the decisions we make.

Keywords: Erdheim-Chester Disease, Medical ethics, Philosophy, Rare diseases, Patient safety

ABBREVIATIONS

CT: Computed Tomography; ECD: Tc-99: Technetium-99; Erdheim-Chester Disease; NSCLC: Non-Small Cell Lung Cancer; LCH: Langerhan's Cell Histiocytosis; HD: Huntington's Disease; WMA: World Medical Association

INTRODUCTION

A middle-aged woman is admitted to the medical floor after being seen in the emergency department for three days of sharp chest pain, along with significant recent weight loss and shortness of breath. Physical exam is unremarkable, but Computed Tomography (CT) of the chest reveals a large mass in the upper lobe of the left lung growing into the mediastinum, accompanied by extensive lymphadenopathy. Based on the initial CT, further imaging is performed to investigate for malignancy and metastasis. Among the numerous findings, a contrast CT of the abdomen and pelvis unexpectedly reveals diffuse peri-renal thickening, with soft tissue encasing both kidneys, causing them to appear fibrous and "hairy;" an MRI of the head reveals brain lesions; and a full body bone scan with technetium-99 (Tc-99) reveals abnormal uptake in the upper and lower extremities. This leads to consideration of Erdheim-Chester Disease (ECD) as a potential diagnosis; but a biopsy is needed to confirm. A CT-guided biopsy of the mediastinal mass is taken, with expectations of what it will reveal; but the pathology report that returns notes adenocarcinoma, compatible with a primary lung lesion. While the diagnosis does not exclude the concurrent presence of ECD, the usefulness of even exploring further confirmation (by further invasive means) is called into question, due to the significantly higher lethality of lung adenocarcinoma.

WHEN FACED WITH A MEDICAL ZEBRA

For those of us who choose to study medicine, a significant part of the appeal is the ability to use our knowledge and expertise to find solutions to challenging medical questions. We are detectives, collecting clues and putting them together to solve the mystery of what ails a person. We spend our days answering questions about how things work, why they work, and how to fix them when they don't work. Our careers, thus, center around two primary questions: what is it, and how do we treat it? And although many times the answer to the second relies heavily on the first, this is not necessarily always the case. There are times when perhaps we should consider abandoning our search for answers, choosing between our curiosity and something not only more practical, but arguably more humane: the quality of a life. This decision, though it may seem obvious to some, has the potential to create significant cognitive dissonance when we are faced with a pathology that is particularly unusual, the metaphorical "zebra" in a field of horses. The case outlined in this paper represents an instance in which academic curiosity and definitive diagnosis are arguably at odds with the central tenet of medicine, "primum non nocere:" first, do no harm.

In the aforementioned case, there is no ambiguity regarding the presence of Non-Small Cell Lung Cancer (NSCLC); but the presence of this condition does not effectively rule out a potential additional disease process. There are few diseases which present with the unusual pattern of soft-tissue deposition around the kidneys and concurrent lower extremity long bone sclerosis, as seen in this patient, and one of the differentials is particularly rare. ECD, a non-Langerhans histiocytosis, has an unknown incidence and no clear etiology, although an aberrant response to infection has been proposed as a potential cause [1]. The most common clinical manifestations include involvement of long bones (95%), maxillary sinus (50%), large vessels (50%), retroperitoneum (50%), heart (57%), and lungs (46%); however, involvement of all organ systems has been reported. Although radiological evidence-including histiocytic infiltration of perinephric fat (described as "hairy kidneys") and increased Tc-99 uptake in the long bones (both of which were seen in this patient) are highly indicative, ECD can only be definitively diagnosed via biopsy and subsequent immunohistological staining, revealing a proliferation of histiocytes that are positive for CD68 and negative for CD1A, effectively differentiating this disease from Langerhan's Cell Histiocytosis (LCH) [1]. Furthermore, there is no evidence that it is an inheritable genetic disorder.

While it would provide knowledge, taking a biopsy in this case would subject the patient to additional invasive testing that may be unlikely to substantially improve her quality of life or mortality. Although ECD patients treated with interferon therapy were reported

to have an overall 5-year survival of 68%, the 5-year survival rate for stage IVB NSCLC (metastases to the brain) is less than 1% [2].

In light of the patient's proven condition associated with poor prognosis, the primary focus for this patient centered on managing the lung adenocarcinoma.

DISCUSSION

Physicians are often faced with complex and difficult decisions and have to be prepared to face a variety of ethical dilemmas on a regular basis. For instance, if a certain disease is suspected, particularly in the presence of an already existing and more lethal one, should the patient be subjected to further workup, even if testing and confirmation would not alter treatment and survival outcomes for that patient?

Do we present a patient with any and all available information and suggest further testing in order to fully understand every presenting problem? Or does this paternalistic stance overwhelm the patient, in essence bullying them into compliance by way of creating a state of anxiety and confusion, ultimately violating a patient's autonomy?

Patients undoubtedly differ in their willingness to receive information that is unlikely to affect treatment outcomes in a positive way, especially when the knowledge creates significant distress. As in Plato's allegory, once the shadows on the wall are seen for what they are, they cannot be unseen: any knowledge that one acquires regarding one's own fate cannot be unlearned. Ignorance is bliss, and, psychologically, may arguably be healthier than the alternative.

This preference has been demonstrated in predictive testing for Huntington's Disease (HD), for which, to date, no cure exists. In one study, only 50% of patients expressed the desire to know their diagnosis in the hypothetical situation of being at 50% risk of developing HD in the future. About 25% of participants strongly preferred uncertainty to certainty for fear of being unable to cope with the information [3]. The "right not to know," then, is certainly a point worthy of discussion when it comes to patient autonomy [4]. As it stands, informed consent is generally considered to be the standard of care in Western medicine. Healthcare providers are encouraged, if not mandated, to present the patient with all the facts and options available to the best of their knowledge and then let the patient decide the course of their treatment based on that information. Would it thus be reasonable to discuss the availability of testing for a suspected disease, even if it would not affect patient management, no matter the outcome?

There are parallels to be drawn between unnecessary cancer screening and unnecessary testing in established disease, even in the presence of strong clinical suspicion: it has been argued that cancer screening should only be performed if it has scientific merit and the potential to improve a patient's life expectancy or quality of life, and, therefore, screening that has no proven benefit and instead only results in increased patient anxiety should be considered unethical [5].

Yet the fact that the patient in question would not directly benefit from invasive testing for ECD does not necessarily make the proposal unethical, as long as there is adequate informed consent and the potential for misconception as to the nature of the biopsy is minimized. Rights-based theories posit that informed consent makes an otherwise rights-violating act permissible. The patient is presented with a choice, based on all available information, and can act as an autonomous agent. Of course, this assumption becomes problematic when subjects are unable to provide true informed consent, as in the case of research involving children [6]. Binik (2018) argues that the conclusion that "imposition [of risk] without the child's consent is impermissible for children is both counter-intuitive and undesirable", citing the benefits to other children that are to be gained from such studies [6]. In this particular case, the issue did not come into play as the patient was above the age of consent and had full capacity. Informed consent included an open discussion of the fact that the biopsy would not be done as a critical part of medical care (i.e. clinical biopsy), but would primarily serve as a tool to confirm a clinical suspicion and/or to contribute to the relatively sparse body of knowledge surrounding ECD. While there are some (mostly experimental) treatment options for ECD, the fact that there was no intent to alter patient management regardless of outcome (due to the confirmed adenocarcinoma and associated prognosis) essentially would have made it a research biopsy [7]. Before performing a non-clinical biopsy, we must consider its actual benefit to the medical community and future patients. If there is no intent to share any meaningful findings in a way that benefits care providers and patients (be it through discussion, presentations, or publications), then there is little justification or value in performing it (unless the patient requests it). As for any biopsy, the issue of inherent risk has to be made clear to the patient, particularly because it is not outweighed by the promise of potential curative benefit. Risks will vary depending on the site the biopsy is taken from and can range from discomfort to infection, bleeding, or even death in rare cases. It is well established that patients will participate in clinical trials in hope of direct personal benefit; and while this is not a clinical trial in the technical sense, care has to be taken to not tacitly imply a curative underpinning. This is especially true in a case as rare and academically relevant as this one. We should try to shield ourselves from bias and the inclination to sway the patient in a particular direction. An informed decision means that patients have arrived at their decision by consultation with their provider, not under duress or coercion and by understanding and appreciating its risks, benefits and alternatives. As long as this neutrality is maintained and the patient is truly informed about the purpose of the biopsy, it is generally deemed ethically permissible for patients to assume a degree of personal risk in exchange for scientific and academic benefit [8,9].

Ethical guidelines almost universally agree that potential harms to research participants must be outweighed by anticipated benefits. Ethical justification is relatively easy if the patient stands to gain something (medically speaking). However, if there is no direct benefit to participants, there has to be a social value associated with it, in this case the improvement of health outcomes for future patients [10]. Despite a general consensus, codified in research regulations and ethics literature, that patients/research participants must not necessarily stand to gain anything from participation in order for the research to be deemed ethical, certain sets of ethical principles seem to stand in direct contradiction to that notion [11]. The 1964 World Medical Association (WMA) declaration of Helsinki (last revised in 2013), which still represents the most important international code of conduct with regards to human subject research, explicitly places the wellbeing of the individual patient above all other considerations [9]. The International Code of Medical Ethics, adopted by the General Assembly of the WMA at London in 1949 (last amended in 2006) states in principle 8: "While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects" [12]. In

addition, Wikler points out the fact that although the vast majority of researchers agree on the necessity of a favorable "risk to benefit ratio" when it comes to research, this gets obscured when there are different interpretations of what that statement entails [11]. In one view, only benefits to the subject directly serves as justification, while in another view, perceived benefits to society, even at the complete exclusion or even detriment of the research subject, may suffice. What exactly is meant by the phrase "benefits to society" certainly is open to interpretation as well. While "risk" to the research subject has a tangible quality (pain, disability, duress, etc.), "benefits to society" can mean a variety of things (e.g. the study itself helps create new research jobs). It is probably safe to say that most Institutional Review Boards would not view such "benefits" as justifiable reasons to expose human subjects to potential harm, exemplifying the subjectivity of the term.

CONCLUSION

The primary ethical justification for conducting research with human subjects is to benefit society [13]. However, the justification for exposing patients to the risk of certain procedures that have no therapeutic value, but may be beneficial to future patients and the medical community at large, is not always an easy one. Guided by the code of medical ethics of the WMA and the maxim of non-maleficence, healthcare providers in particular are often hesitant to subject their patients to procedures that are not contributive to their care. While these reservations are very valid and understandable, it is nonetheless important to consider the fact that the "risk-benefit" of testing does not solely apply to the benefits of the individual themselves. Instead, we have to also consider benefits in terms of scientific advancement and future patients. In other words, a favorable outcome for the research participant is not an absolute ethical requirement because in patients with capacity, informed consent makes involvement in research with no direct benefit to the participant permissible. In certain cases, even the absence of consent (e.g. research involving children and during emergency management) is no absolute contraindication, so long as the risk to patients is reasonably minimized and there is considerable societal benefit (in terms of improved outcomes for future patients) that can be identified. After a very detailed discussion, the patient consented to a superficial biopsy, which was consistent with ECD. She was pleased to learn that she was able to further advance medical knowledge and potentially help future patients. Through her altruism and selflessness, she was able to celebrate a small victory, despite the bleakest of prognoses.

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