

BEYOND BAYES

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Case report

A 64-year-old man was brought to the emergency room for the sudden onset of diplopia. Nausea, dysarthria, and weakness in the left limb were also reported. Neurologic examination showed a convergent strabismus due to internal rotation of the right eye, along with right facial paresis and a weakness involving the left arm and leg. A diagnosis of right lateral medullary lesion, i.e. Wallenberg's syndrome, was made; a CT scan of the head showed a well-defined hemorrhagic bulbopontine lesion. The patient was admitted to the general medicine ward.

When I first saw the patient, I was struck by his plethoric face and a deep peripheral cyanosis. Blood pressure (130/85 mmHg) and temperature (37.2°C) values were not relevant. History taking revealed that the patient was a heavy smoker (two packs of cigarettes a day) and had been submitted to a lumbar gangliectomy two years before for left leg claudication. For two months he had complained of malaise, had experienced episodes of sweating and rash and had lost 2 kg.

Physical examination proved to be extremely informative. Palpation of the abdomen disclosed a large, irregular, stiff mass extending 15 cm below the left costal margin. There was no hepatomegaly or lymphadenopathy. The laboratory results provided some odd hints: hematocrit 59.5 percent, hemoglobin 19.7 g per deciliter, 12.7×10^9 white cells per liter with 82 percent polymorphonuclear leukocytes, 10 percent lymphocytes, 2 percent eosinophils and 1 percent monocytes, platelets $583 \times 10^9/L$. The erythrocyte sedimentation rate was 8 mm per hour. Urinalysis showed 1+ protein, 2 to 5 white cells and 2 to 5 red cells per high-power field, and 1 coarse granular cast. Other laboratory

examinations were normal. The chest film was clear, and the electrocardiogram was unremarkable except for voltage changes consistent with left ventricular hypertrophy.

I tackled the new problems one at a time. A clue was the polyglobulia. At further history taking, I found no incidence of polyglobulia in the family; the patient had not suffered from pruritus or erythromelalgia, and had not had any laboratory examinations in the last two years. The patient smoked, which is a cause of polyglobulia, mostly relative in nature, i.e. due to reduced plasma volume. However, with a hematocrit of 59 percent I did not consider that a relative polyglobulia was the problem here, and I ascribed such a marked polyglobulia to increased red cell production. Since erythropoiesis is driven by an oxygen-dependent feedback, I ordered arterial blood gas analysis, a simple, quick and reliable test. With the patient breathing room air, the values of the arterial blood gases were as follows: pH 7.4; partial pressure of oxygen 85 mm Hg; and partial pressure of carbon dioxide 43 mm Hg. Arterial oxygen saturation was 96 percent.

The second clue was the left abdominal mass. The abdominal CT scan showed a solid mass 9×10 cm in diameter, heterogeneous and vascularized, originating from the left kidney; this was consistent with a renal tumor. No regional lymph nodes were documented. The spleen retained normal dimensions.

On further testing, a blood smear revealed the presence of platelet aggregates, no anisocytosis and a normal differential without immature cells. The leukocyte alkaline phosphatase score was normal. α_2 -globulin was 1.08 g per deciliter (normal <0.8), C-reactive protein was 1.26 mg per deciliter (normal <0.6). Fibrinogen and

serum iron were normal. A hematological examination repeated four days later revealed: hematocrit 64.4 percent, hemoglobin 20.9 g per deciliter, 22×10^9 white cells per liter, platelets $516 \times 10^9/L$.

I felt the case was ever more intricate than I first suspected. CT scan is reliable for both diagnostic certainty and staging of renal cancer. Thus the patient did not need any other investigations for this. The fever, elevated C-reactive protein and $\alpha 2$ -globulin level suggested that the patient had an active inflammatory process, and I attributed this process to the renal cancer. The normal blood gas values and normal oxygen-hemoglobin affinity ruled out the possibility that polyglobulia was due to defective tissue oxygenation. The age of the patient and the absence of family history allowed me to exclude rare forms of congenital or essential polyglobulia. I now considered the case as that of a man having a hemorrhagic stroke, an absolute non-hypoxic polyglobulia, a modest increase in leukocytes and platelets without splenomegaly, and a renal tumor associated with signs of inflammation and fever.

I had been keeping clearly in mind the criteria for a diagnosis of polycythemia vera issued by the *Polycythemia Vera Study Group* (PVSG). According to these criteria, a diagnosis of polycythemia vera is tenable if significant erythrocytosis, normal blood oxygenation and splenomegaly are all present. When splenomegaly is absent, two of the followings are necessary: significant leukocytosis in the absence of fever, increased platelet count, and increased leukocyte alkaline phosphatase score. Increased vitamin B12 level was originally included in the list, but now its importance has been re-evaluated.

Our patient exhibited only two of these major criteria (erythrocytosis and absence of hypoxia). Fever and inflammation made the significance of leukocytosis at best doubtful. Thus, in strict observance of the PVSG criteria, a diagnosis of polycythemia vera was not tenable. The Group stressed that quite a high number of false negatives could be observed with these criteria, but the absence of symptoms such as aquagenic pruritus or erythromelalgia made the diagnosis even more unlikely. The fact is that in this

patient all of these hematologic alterations were also consistent with a paraneoplastic syndrome associated with the renal tumor. A renal tumor produces high quantities of cytokines, in particular IL-1, IL-6 and TNF, that cause fever, leukocytosis and thrombocytosis. On the other hand, a renal tumor may also produce an inappropriately high quantity of erythropoietin that causes polyglobulia. Even though I could not completely rule out polycythemia vera, I tended to tie all these findings together. I thought that the patient had only one disease associated with stroke, i.e. a renal tumor with a paraneoplastic hematologic syndrome.

However, even though I was confident that the patient did not have polycythemia vera, I found a number of reasons for continuing with these examinations. The persistence of polyglobulia after the removal of renal cancer, as would happen in the case of polycythemia vera, had to be considered both for the patient's awareness and for the follow-up of the cancer itself. Without specific treatment the presence of polycythemia vera would make the risk of a new vascular accident exceedingly high. In conclusion, I requested a serum erythropoietin level assay and proposed that the hospital's hematology research laboratory study the growth pattern of the patient's circulating erythroid progenitor cells. The serum erythropoietin was 3 mU per mL (normal 5 to 25) and was considered to be diagnostic of polycythemia vera.

The patient was venesected until a hematocrit of 42 percent was reached and then sent to a surgeon. The renal mass was operated upon, and histological examination revealed a renal cell carcinoma. The postoperative course was uneventful. The results of erythroid progenitor growth were available after surgery. They documented growth of circulating erythroid precursor cells in the absence of erythropoietin. Six months after surgery, the patient has nearly completely recovered from the stroke and is receiving hydroxyurea for polycythemia vera.

Comments

The incremental nature¹ of a physician's reasoning is well adapted to cases which seem plain

at the outset, but prove to be unexpectedly intricate as the results of clinical investigations accumulate. Breaking down each patient's diagnostic problem into small stages permits sophisticated reasoning with limited computational resources. The physician caring for the patient in this case made his incremental reasoning explicit, facilitating a cognitive interpretation.

It is apparent that the physician was so struck by the clarity of the presentation of the patient that he felt at ease in formulating a diagnosis of Wallenberg's syndrome with a pattern recognition mechanism. Then, when new clinical data that were inconsistent with this diagnosis appeared, he easily constructed a new problem space: an incidental renal tumor with absolute non-hypoxemic polycythemia, leukocytosis and thrombocytosis without splenomegaly. Finally, he generated new hypotheses of a paraneoplastic syndrome due to the renal tumor, or of a polycythemia vera associated with the renal tumor. What was difficult in this case was the closing phase of the diagnosis.

Incidentally finding two rare diseases is not an everyday event for a physician. The incidence of renal cancer is 7 for 100,000 men and 3 for 100,000 women,^{2,3} thus 50 times less frequent than lung cancer in males and breast cancer in females of the same age.⁴ Polycythemia vera is an even rarer disease; the highest incidence figure recorded is 1.6 for 100,000.⁵ Modern medicine leads more and more to the discovery of diseases in their earlier silent phases, making traditional diagnostic criteria obsolete. Almost 1 in 2 renal cancers are now incidentally detected at routine health examination or during examinations of unrelated diseases.^{6,7} Similarly, 17 to 26 percent of patients with polycythemia vera are diagnosed fortuitously or due to complications of the disease.⁵

The physician caring for the patient in question claimed to be taxed from all these rarities, and he had to draw on all his clinical acumen to resolve the diagnosis. Nobody, we think, would have had the solution at hand; pattern recognition was of no help in this case.

How did the physician arrive at the diagnosis? A linear path of diagnostic actions is apparently displayed; he requested an exhaustive series of

tests that led to the diagnostic one. But what makes this case exemplary is that the diagnostician's thought process discloses a pathway to the closing phase of the diagnosis that was by no means unidirectional. First, he claimed that the findings indicated a paraneoplastic syndrome, then he changed his diagnosis to the right one.

It seems clear that the physician used a reasoning modality based on logical considerations as to how the evidence fit with existing knowledge of the disease. This is mainly an exercise of a probabilistic nature. In the case of this man, the diagnostician had to assign a probability to polycythemia vera in the presence of a renal cancer. The doctor used the diagnostic rules for polycythemia vera that were proposed by the PVSG in 1975⁸ and revised by representatives of the French Society of Hematology in 1994.⁹ The low diagnostic score due to the absence of splenomegaly and the uncertain nature of the leukocytosis because of the concurrent fever caused the doctor to use additional symptoms, such as pruritus and erythromelalgia, to rule out PV. In the end, since the situation presented by the patient could also be completely justified by a paraneoplastic syndrome, he was satisfied with this last diagnosis.

Faced with the difficult nature of probability, physicians prefer to navigate through the inferences of decisional tasks by using a series of heuristic hypotheses. Actually, in this case, the cognitive measure used was the merging of completeness with simplicity. Completeness provides a measure of the symptoms that a hypothesis explains, while simplicity regards the hypotheses that a set of findings explains. Here, the physician put a higher value upon the criterion of simplicity, adopting the principle of Ockham's razor, proposed by the 14th-century philosopher, which states that *«entities are not to be multiplied beyond necessity»*. Translated into medical practice, if a single explanation is sufficient, then there is no reason to postulate a second. This principle, which may be read in the classical books of medicine, is taught in medical schools and is applied with proficiency in everyday clinical practice.

What is the computational counterpart to this segment of reasoning? How could formal prob-

lem-solving methods help in resolving this dilemma?

Renal tumors produce polyglobulia in 5 percent of cases,¹⁰ and leuko-thrombocytosis in 5 to 20 percent of cases¹¹ (say 12.5). Thus, assuming the independence of these symptoms, the probability that this patient's hematologic syndrome could have been due to the renal cancer approximates 6.2 per thousand (5 percent times 12.5 percent). Polycythemia vera occurs without splenomegaly in 19 to 50 percent of cases, with leuko-thrombocytosis in 32 to 84 percent.⁵ Approximating these figures to their mean value, the probability that the hematologic syndrome could have been due to the polycythemia vera is 20.3 percent (35 percent times 58 percent). Bayes' rule updates the probability of polycythemia vera in the general population (its prevalence) to that of our patient. The incidence of polycythemia vera in the general population is about 1 case every 100,000.⁵ Assuming that a patient with polycythemia vera remains a prevalent case until death, a 10-year median survival⁵ produces a prevalence of 10 per 100,000.¹² Thus, using the figures reported above and calculating Bayes' revised probability in tabular form (Table 1), the probability that the patient has a polycythemia vera is around 3 per thousand. The probability of pruritus or erythromelalgia in polycythemia vera patients approximates, respectively, 28.5 and 5.5 percent.⁵ Due to the very low sensitivity of these findings, revising the probability of polycythemia vera for their absence modifies the result minimally in this patient.¹³ In conclusion, the diagnostician employs heuristic reasoning to arrive at a rational diagnostic conclusion. Unfortunately it is wrong. The high probability of false negative results with PVSG guidelines, which were in fact

recommended for sake of homogeneity in clinical trials, leads to the exclusion of atypical and early forms of the disease.

In our formal analysis of the diagnostic reasoning process, a second phase can be recognized at this point. The physician sought to eliminate uncertainty from the diagnosis and explicitly stated his reasons for doing so. This impelling imperative is easily recognized by its utilitarian nature; the minimal chance of overlooking a polycythemia vera became clinically relevant, which is why additional diagnostic parameters were assessed. A serum erythropoietin level assay and the study of the circulating hemopoietic progenitor cell are usually unnecessary examinations for the diagnosis of polycythemia vera. Serum erythropoietin level does not perfectly discriminate patients with polycythemia vera and secondary erythrocytosis.^{14,15} The study of erythroid colonies is a promising examination in spite of its limited availability and difficult standardization. The growth of erythroid colonies in the absence of erythropoietin has been demonstrated to be a highly sensitive, albeit poorly specific, criterion.¹⁶ In the case of this man, a low serum erythropoietin level combined with spontaneous growth of erythroid colonies excluded false positive results and unquestionably proved the diagnosis.

Even though there was a very low probability of mistaking the diagnosis, the physician ascribed a great value to his fear of prematurely excluding another possibility. It has been hypothesized that physicians make decisions by avoiding medical actions which are most likely to lead to regret. A *chagrin factor* has been proposed as an internal measure of regret for the outcome.¹⁷ In the case of this patient, testing that revealed the absence of polycythemia vera would produce the *chagrin*

A	B	C	D	E
Disease state	Prior probability of disease	Conditioned probability of findings	Product (BxC)	Posterior probability of disease (D/sumx100)
PV present	0.0001	0.203*	0.0000203	0.3
PV absent	0.9999	0.0062	0.0061993	99.7
Sum = 0.0062196				

Table 1. Using Bayes' rule to calculate the probability of polycythemia vera in a patient with renal tumor and polyglobulia, modest leuko-thrombocytosis and the absence of splenomegaly.

PV: polycythemia vera.

*In the case of polycythemia vera present, the findings were assumed to be due only to polycythemia vera.

of having ordered an unnecessary and relatively costly test. Without testing, one is threatened by the possible presence of polycythemia vera. In conclusion, the chagrin of a premature final diagnosis with no further testing was judged to be extremely high in this case, justifying the physician's decision to continue investigating even in the presence of a very low likelihood of the disease.

The crucial lesson in this patient's case is that a feeling of uncertainty is an intrinsic part of clinical practice; this sometimes causes physicians to expose their patients to serious risk and other times to consume resources for unproductive studies. However, it is also of key importance to continue searching in order to avoid prematurely excluding other possibilities. The incremental nature of reasoning enables physicians to engage in the master paradigms of medical decision making: probability and utility. Ockham's razor, based on the criterion of simplicity, attracts physicians who can use it as a shortcut in weighting out probability but, as we have seen and as others have reported,¹⁸ it may not always produce accurate results. The expert physician, as our proved to be, is one who is willing to abandon results derived from probabilistic reasoning for the satisfaction born of utility.

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