Limited value of elevated erythrocyte sedimentation rate as an indicator of malignancy

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Background. Patients with an elevated erythrocyte sedimentation rate (ESR) are often suspected of having malignant disease and are subjected to extensive investigations. Thus, the finding of an elevated ESR can result in considerable costs and might even be dangerous for the patient if invasive studies are ordered.

Objectives. Our aims were to establish (i) the prevalence of malignant diseases in hospitalized patients and out-patients with elevated ESR; and (ii) the long-term incidence of malignant diseases in patients during 5 years after unsuccessful investigation for elevated ESR.

Methods. A cross-sectional survey was carried out in 128 patients admitted to the Department of General Internal Medicine, University of Kiel and in 94 out-patients under the care of a GP. A retrospective cohort study of 50 patients was also carried out by contacting GPs of patients discharged from hospital after unsuccessful investigation.

Results. In the hospitalized patients, the ESR was elevated in 53.1% (68/128) and was normal in 46.9% (60/128). Malignancy was found in 25.0% (17/68) of patients with elevated ESR and in 15% (9/60) of patients with normal ESR (P = 0.16). Of the out-patients, 94 patients with elevated ESR were investigated, of whom 8.5% (8/94) had malignancies (P = 0.004 compared with hospitalized patients). In the follow-up study of 50 patients who had been discharged with the diagnosis ‘elevated ESR of unknown origin’, follow-up information was available from 38 individuals. Of these, 71.0% (27/38) had not developed signs or symptoms of any disease at the time of investigation. Malignant disease had developed in only 5.3% (2/38).

Conclusion. The prevalence of malignancy in patients with elevated ESR is low, in both the clinical and the general practice setting. Elevation of ESR is not an early sign of malignant disease and does not justify extensive investigation in a patient who has no symptoms which are suggestive of a tumour.

Keywords. Erythrocyte sedimentation, indicator, malignancy, prevalence.

Introduction

The erythrocyte sedimentation rate (ESR) is one of the oldest and most frequently utilized laboratory methods.1 For the patient, a ‘normal ESR’ indicates the absence of serious pathology, a view that is shared by many doctors. On the other hand, patients with an elevated ESR are often suspected of having a malignant disease and are subjected to extensive investigations. Thus, the finding of an elevated ESR can result in considerable costs and might even be dangerous for the patient if invasive studies are ordered.

Measurement of the ESR is commonly accepted to be of diagnostic value if certain diseases are suspected on clinical grounds, e.g. polymyalgia rheumatica or plasmocytoma. It is, however, less clear whether extensive investigation should be performed in a patient with elevated ESR but no symptoms suggestive of malignancy.

The present study was designed to (i) find out the prevalence of malignant diseases in individuals with elevated ESR among hospitalized patients and in patients seen by a GP; and (ii) obtain information on the long-term outcome of patients discharged from hospital with the diagnosis ‘elevated ESR of unknown origin’.
Methods

Part A

A cross-sectional study was performed on all in-patients in our clinic (a tertiary care medical centre) on a certain day (9 September 1997). They had been admitted for various reasons and the ESR had been determined as a routine procedure on admission. We then divided the patients into two groups (ESR either elevated or normal) and analysed the prevalence of malignant diseases in these two groups.

In order to compare these results with those obtained in a general practice setting, the charts of patients with elevated ESR who had been seen by a GP between 3 June and 6 August 1996, were reviewed. The prevalence of malignant diseases was evaluated.

Part B

Patients who had been admitted to our hospital for evaluation of elevated ESR between 1 January 1990 and 31 December 1992 were investigated. All patients had been discharged with the diagnosis ‘elevated ESR of unknown origin’. By contacting the primary care physician, we sought to determine what diagnosis, if any, had emerged during the subsequent 5 years.

In all studies, an ESR of >10 mm/h was considered elevated.

Statistics

Statistical evaluation of the data was performed using the chi-square test with $P < 0.05$ being accepted as statistically significant. Proportions are given with 95% confidence intervals (CI).

Results

Part A

A total of 128 hospitalized patients were investigated. The ESR was elevated in 68 patients (53.1%) and was normal in 60 (46.9%).

Malignancy was found in 25.0% (17/68) of patients with elevated ESR (CI 14.7–35.3%) and in 15% (9/60) patients with normal ESR (CI 10.4–19.6%). This difference was not statistically significant ($P = 0.16$). All malignancies in the group with normal ESR were solitary tumours, whereas in the group with elevated ESR four of 16 tumours were either lymphomas ($n = 3$) or plasmocytoma ($n = 1$).

Ninety-four patients with elevated ESR seen in a general practice were investigated. Of these, 8.5% (8/94; CI 6.2–10.8%) had malignancies ($P = 0.004$ compared with hospitalized patients).

Part B

Of the 50 patients who had been discharged with the diagnosis ‘elevated ESR of unknown origin’, follow-up information was available from 38 individuals. Of these, 71.0% (27/38; CI 57–85%) had not developed signs or symptoms of any disease at the time of investigation. An unequivocal correlation of the persistently elevated ESR with malignant disease could be established in only 2/38 cases, one of which was gastric carcinoma and the other recurrent breast cancer. All other patients suffered from a variety of conditions usually not considered to be associated with elevated ESR.

Discussion

More than 70 years after its introduction into clinical medicine by Westergren, the ESR is still in use as a simple and quick laboratory test. According to common practice, it is considered predominantly to be an indicator of inflammatory or malignant disease. Recently, the method has aroused new interest since it might be of prognostic value in coronary artery disease and stroke.

It is, however, a common misconception to think that the ESR is a relatively inexpensive laboratory test. The problem with ESR, as with many other laboratory investigations which are ordered routinely, is that an abnormal finding may generate further investigations, which are then expensive, hazardous and frequently unrewarding.

The aim of the present study was not to re-evaluate the usefulness of ESR when chosen for the correct purposes. We also did not intend to reiterate the extensive discussion on the superiority of either C-reactive protein or ESR for screening and monitoring of inflammatory disease. Rather, we were interested in the significance of an elevated ESR as an early indicator of malignancy and, secondly, in the final diagnosis of patients who undergo unsuccessful clinical investigation for elevated ESR. There is only one study in the literature providing follow-up data on patients with elevated ESR. However, that study was designed to evaluate the 1-year morbidity and mortality of elderly people with grossly elevated ESR. Patients had been followed-up for only 1 year, and the diagnosis was already known in some patients when the elevated ESR was found. To our knowledge, our investigation is the first attempt to determine the incidence of malignant disease in the long term in patients having undergone extensive but unsuccessful clinical work-up for elevated ESR.

In hospitalized patients with elevated ESR, malignancies were found in 25% of all cases, which was not significantly different from the incidence of malignancies in patients with normal ESR. This clearly demonstrates that measuring ESR is of no value as a screening procedure for malignant disease. The consequence of this is that a raised ESR should not trigger diagnostic procedures to find evidence of malignancy if the patient has no other symptoms suggestive of a tumour.

In patients with elevated ESR seen by a GP, the prevalence of malignancy is even less (8.5%), probably...
due to a larger portion of patients with common infectious diseases. It must be stressed that the data used to compare disease prevalence between the hospital and general practice settings relate to different time periods which are over a year apart. Although the validity of the analysis therefore potentially is compromised, we assume that the prevalence of elevated ESR is unlikely to be influenced to a large extent by any other confounders during a 1-year period.

More importantly, the low incidence of malignant disease in patients previously investigated in the hospital for elevated ESR indicates that it is not useful to focus on malignant disease in these patients. Certainly, a number of conditions typically associated with elevated ESR need to be excluded, e.g. plasmocytoma. However, this can be achieved with reasonable effort and cost.

In order to understand the limitations of ESR measurement for the differentiation between ‘healthy’ and ‘sick’, one has to recall that the ESR, unlike most other laboratory tests, reflects the interaction of numerous blood components, not all of which have been fully recognized. Basically, the two major determinants of ESR are erythrocyte aggregation and haematocrit. Red blood cell aggregation, in turn, is influenced by plasma proteins, which reduce the negative electrostatic forces between red cells, causing aggregation and faster sedimentation. If one considers the enormous variability in plasma protein composition and interaction, it is clear that a high variability of test results must ensue. Accordingly, it has been found that ESR, in the absence of any disease, is influenced by obesity, age and race. ESR is always slightly raised in anaemia, a fact that is not appreciated in many patients, as well as due to the influence of drugs.

Recently, it was proposed by some groups that systematic ESR recording over time could enable the physician to note a rising trend, which could provide an early clue to another otherwise non-symptomatic disease, in particular renal cell carcinoma. The perceived benefit of this approach, however, would constitute an enormous financial burden on the community, with a questionable benefit for the patient.

We conclude from our findings that the measurement of ESR is not a valuable screening procedure for establishing the presence or absence of malignant disease. If elevated, it provokes anxiety, if normal, it implies good health, neither of which are necessarily in the patient’s interest. ESR, like any other laboratory test, should be used judiciously, e.g. to confirm a suspected diagnosis which is based on clinical findings or to monitor disease activity.

References