Atypical cells in Sysmex UN automated urine particle analyzer: a case report and pitfalls for future studies

Abstract

Objectives: Sysmex UN series fully automated urine analyzer reports a series of research parameters besides routine parameters including the “atypical cells” parameter. An automated instrument in clinical use capable of detecting neoplastic cells of the urinary tract will have paramount significance.

Case presentation: A 73 years old male patient with a recurrent high grade urothelial carcinoma admitted to our urology outpatient clinic due to hematuria.

Urinalysis showed +3 hemoglobin, +3 leukocyte esterase, 200/HPF red blood cells, 300/HPF white blood cells. The instrument also reported atypical cells (7.6/µL or 1.3/HPF) under the heading of “research parameters.” Presence of atypical cells was confirmed by the manual microscopy. The patient has undergone transurethral resection of papillary lesions and the pathology report confirmed a recurrence. On follow-up, atypical cells fell to 0.1/µL after 40 days.

Conclusions: This case report presents a patient with atypical cells in urine, detected by a fully automated urine analyzer. The atypical cells presented on the screen of the analyzer were confirmed by the manual microscopy. This presentation may influence future studies pertaining to the subject.

Keywords: atypical cells; automated analyzer; cancer; cut-off value; decision limit; reference interval; urinalysis; urinary sediment; urine; urothelial carcinoma.

Introduction

Automation in laboratory evolves at an enormous scale. Laboratories without any human intervention are not fiction.
any more. High performance instruments and on-line pre-analytic devices have already driven technical stuff to extinction. Struggle in the analytic phase seems to be over in clear advantage of machines. Auto-verification of test results is the next front line where efficient software systems face with human intelligence. It is not odd to define some machine work as artificial intelligence. Perhaps the most close to the definition are the urinalysis instruments. The software systems of these machines are programmed to define particular cell types in the urine as much alike the way human brain does. Some of them use optic lenses built inside to “see” while some others use laser beams and voltage sensors to compose a sense of “vision.” The visions are then evaluated by a software system that labels the cells to compose a report. Of concern, last generation devices dare to add clinical diagnosis estimations to their reports. These instruments are faster than us, accepted to be more reliable than us and finally they are evolving to be smarter. At this process, manufacturers should not be left alone. Turn-backs than us and finally they are evolving to be smarter. At this process, manufacturers should not be left alone. Turn-backs than us and finally they are evolving to be smarter.

Sysmex UN series fully automated urine particle analyzer is a promising instrument. The modular Sysmex UN-Series (Sysmex Corporation, Kobe, Japan) offers variable combinations of instruments. The UC-3500 uses test strips for chemical analysis of the urine. UF-4000/5000 uses fluorescence flow cytometry technology and hydrodynamic focusing for urine sediment analysis, where particles are stained by specific fluorochromes for nucleic acids and surface structures and then sent through the semi-conductor laser beam. Counting and classification is based on signals of scattered light and fluorescence to determine the characteristics of the particles. Atypical cells show side fluorescence and scattered light properties indicating their enlarged nuclei and increased nucleus/cytoplasm ratio. If more investigation of certain particles is requested UD-10 presents images captured by an internal camera. Sysmex UN-Series reports a series of research parameters besides routine parameters. These parameters are reported for every sample presented to the instrument but are not validated or sent to the laboratory information system. Perhaps the most challenging parameter is the “atypical cells” parameter. Urine samples sent to the laboratory for any reason may contain neoplastic cells of the urinary tract. An automated instrument in clinical use which is able to detect suspicious neoplastic cells will have paramount significance.

Case report

A 73 years old male patient admitted to our urology outpatient clinic due to hematuria. The patient was alert about hematuria as he had already undergone transurethral tumor resection for malignant urothelial neoplasm for 3 times in 14 months. Urinalysis showed chemical and cytological features of gross hematuria and urinary tract infection. On cystoscopy examination, mucosal irregularities and papillary formations were observed in 2 × 5 cm area. The lesions were excised and pathology report informed a high grade urothelial neoplasm invading the lamina propria of urinary bladder.

The pre-op urine sample was examined by the Sysmex UN Series automated analyzer. In addition to routine parameters, the UF-4000 particle analyzer reported atypical cells (7.6/µL or 1.3/HPF) under the heading of “research parameters.” The sample was manually sent to the modular Sysmex UD-10 instrument for cellular images and a portion of urine was prepared for manual microscopic examination. The research parameters including the “atypical cells” were not presented on the patient test results page.

After performing the automated sediment testing by the instrument, the residual urine specimen was collected for manual microscopic examination. The urine was centrifuged at 1,500 rpm for 5 min, supernatant was discarded, and the remaining material was stained with modified Sternheimer urine sediment stain. On manual microscopic evaluation; the sample was crowded with red and white blood cells in line with the automated analyzer. In addition, very large cells forming small groups or distributing as single cells could be observed even at the low power field examination. At high power examination, these cells with big nuclei and prominent nucleolus were reminiscent of photographed cells in Sysmex UD-10 analyzer as atypical cells (Figure 1).

Discussion

Neoplastic cells originated from the urinary tract can rarely be found in urine samples sent to the laboratory. Only a high index of suspicion and experience in tumor cytology can identify these cases [2]. In 2013 we defined atypical cells (probably neoplastic) in urine sediment analysis by a poster presentation in a national congress [3]. We suggested that automation, digital imaging and artificial intelligence had kept a potential. Our foresight seems to come true: Sysmex UN series are currently working in our central laboratory and the instrument reports atypical cells as a research parameter. As expected, literature pertaining to the subject is scarce so that there is no reference in hand to call a result of the analyzer as high, normal or low. Patient results in this parameter are generally lower than 1.5/µL and results higher than 2.5/µL are rare [unpublished data].
A research parameter is by definition needs detailed studies to prove its clinical value. Atypical cells parameter has some handicaps. First of all and most importantly, evaluating these cells necessitates personnel with capability in cytology. While all automated urine analyzers suggest on board user editing, differential diagnosis of atypical cells is quite apart from editing routine urinalysis parameters. In our case report, identity of cellular images from the UD-10 analyzer and in manual microscopy had to be confirmed by a pathologist. First question to be answered is: how adequate or satisfactory will it be to define a cut-off value of atypical cells to be considered as a decision limit for risk of cancer? A positive test result will make a cystoscopy or an ultrasonography necessary.

Alternatively, all specimens with a higher value than the decision limit should be sent to UD-10 analyzer for visual editing. However editing these samples needs extra knowledge and experience in cytology. Actually, Sysmex UF 4000 unit reports a numeric value of atypical cells but UD 10 unit does not mark the visualized cells so that editing action is estimation.

It is likely that researchers will focus on defining a decision limit that hopefully defines samples with a suspicion of malignancy. Meanwhile, the machine software needs to be up-graded to generate “smarter” instruments. At this point, our case poses a perfect example of case study. The software must be handled as an artificial intelligence to be structured or from a practical point of view as a child to be educated. Cases like ours will serve in teaching true positives while some others are needed to define false negatives. Studies should include pathologists, urologists and radiologists besides laboratory specialists.

In conclusion, a machine in a laboratory which is capable of defining a suspicion of malignancy from a urine sample will save lives. Malignant cells detached from a tumorous lesion are present in urine of patients with an urothelial carcinoma. Any particle existing in a urine sample can possibly be detected. There will be problems and instrument software evolution needs human guidance. Our case report will hopefully inspire future studies.

**Conflict of interest:** none declared.

**References**